

VPI96-01 CIP2

INHIBITORS OF INTERLEUKIN-1 β CONVERTING ENZYMEINS
ALTECHNICAL FIELD OF THE INVENTION

The present invention relates to novel
5 classes of compounds which are inhibitors of
interleukin-1 β converting enzyme ("ICE"). This
invention also relates to pharmaceutical compositions
comprising these compounds. The compounds and
pharmaceutical compositions of this invention are
10 particularly well suited for inhibiting ICE activity
and consequently, may be advantageously used as agents
against interleukin-1- ("IL-1"), apoptosis-, interferon
gamma inducing factor- ("IGIF") and interferon- γ -
("IFN- γ ") mediated diseases, including inflammatory
15 diseases, autoimmune diseases, destructive bone,
proliferative disorders, infectious diseases and
degenerative diseases. This invention also relates to
methods for inhibiting ICE activity, and decreasing
IGIF production and IFN- γ production and methods for
20 treating interleukin-1-, apoptosis-, IGIF- and IFN- γ -
mediated diseases using the compounds and compositions
of this invention. This invention also relates to
methods of preparing N-acylamino compounds.

- 2 -

BACKGROUND OF THE INVENTION

Interleukin 1 ("IL-1") is a major pro-inflammatory and immunoregulatory protein that stimulates fibroblast differentiation and proliferation, the production of prostaglandins, collagenase and phospholipase by synovial cells and chondrocytes, basophil and eosinophil degranulation and neutrophil activation. Oppenheim, J.H. et al, Immunology Today, 7, pp. 45-56 (1986). As such, it is involved in the pathogenesis of chronic and acute inflammatory and autoimmune diseases. For example, in rheumatoid arthritis, IL-1 is both a mediator of inflammatory symptoms and of the destruction of the cartilage proteoglycan in afflicted joints. Wood, D.D. et al., Arthritis Rheum. 26, 975, (1983); Pettipher, E.J. et al., Proc. Natl. Acad. Sci. UNITED STATES OF AMERICA 71, 295 (1986); Arend, W.P. and Dayer, J.M., Arthritis Rheum. 38, 151 (1995). IL-1 is also a highly potent bone resorption agent. Jandiski, J.J., J. Oral Path 17, 145 (1988); Dewhirst, F.E. et al., J. Immunol. 8, 2562 1985). It is alternately referred to as "osteoclast activating factor" in destructive bone diseases such as osteoarthritis and multiple myeloma. Bataille, R. et al., Int. J. Clin. Lab. Res. 21(4), 283 (1992). In certain proliferative disorders, such as acute myelogenous leukemia and multiple myeloma, IL-1 can promote tumor cell growth and adhesion. Bani, M.R., J. Natl. Cancer Inst. 83, 123 (1991); Vidal-Vanaclocha, F., Cancer Res. 54, 2667 (1994). In these disorders, IL-1 also stimulates production of other cytokines such as IL-6, which can modulate tumor development (Tartour et al., Cancer Res. 54, 6243 (1994). IL-1 is predominantly produced by peripheral blood monocytes as part of the inflammatory response

- 3 -

and exists in two distinct agonist forms, IL-1 α and IL-1 β . Mosely, B.S. et al., Proc. Nat. Acad. Sci., 84, pp. 4572-4576 (1987); Lonnemann, G. et al., Eur. J. Immunol., 19, pp. 1531-1536 (1989).

5 IL-1 β is synthesized as a biologically inactive precursor, pIL-1 β . pIL-1 β lacks a conventional leader sequence and is not processed by a signal peptidase. March, C.J., Nature, 315, pp. 641-647 (1985). Instead, pIL-1 β is cleaved by
10 interleukin-1 β converting enzyme ("ICE") between Asp-116 and Ala-117 to produce the biologically active C-terminal fragment found in human serum and synovial fluid. Sleath, P.R., et al., J. Biol. Chem., 265, pp. 14526-14528 (1992); A.D. Howard et al., J.
15 Immunol., 147, pp. 2964-2969 (1991). ICE is a cysteine protease localized primarily in monocytes. It converts precursor IL-1 β to the mature form. Black, R.A. et al., FEBS Lett., 247, pp. 386-390 (1989); Kostura, M.J. et al., Proc. Natl. Acad. Sci. UNITED STATES OF
20 AMERICA, 86, pp. 5227-5231 (1989). Processing by ICE is also necessary for the transport of mature IL-1 β through the cell membrane.

ICE, or its homologs, also appears to be involved in the regulation of programmed cell death or
25 apoptosis. Yuan, J. et al., Cell, 75, pp. 641-652 (1993); Miura, M. et al., Cell, 75, pp. 653-660 (1993); Nett-Fiordalisi, M.A. et al., J. Cell Biochem., 17B, p. 117 (1993). In particular, ICE or ICE homologs are thought to be associated with the regulation of
30 apoptosis in neurodegenerative diseases, such as Alzheimer's and Parkinson's disease. Marx, J. and M. Baringa, Science, 259, pp. 760-762 (1993); Gagliardini, V. et al., Science, 263, pp. 826-828 (1994).
Therapeutic applications for inhibition of apoptosis

- 4 -

may include treatment of Alzheimer's disease, Parkinson's disease, stroke, myocardial infarction, spinal atrophy, and aging.

ICE has been demonstrated to mediate
5 apoptosis (programmed cell death) in certain tissue
types. Steller, H., Science, 267, p. 1445 (1995);
Whyte, M. and Evan, G., Nature, 376, p. 17 (1995);
Martin, S.J. and Green, D.R., Cell, 82, p. 349 (1995);
Alnemri, E.S., et al., J. Biol. Chem., 270, p. 4312
10 (1995); Yuan, J. Curr. Opin. Cell Biol., 7, p. 211
(1995). A transgenic mouse with a disruption of the
ICE gene is deficient in Fas-mediated apoptosis (Kuida,
K. et al., Science 267, 2000 (1995)). This activity of
ICE is distinct from its role as the processing enzyme
15 for pro-IL1 β . It is conceivable that in certain tissue
types, inhibition of ICE may not affect secretion of
mature IL-1 β , but may inhibit apoptosis.

Enzymatically active ICE has been previously
described as a heterodimer composed of two subunits,
20 p20 and p10 (20kDa and 10kDa molecular weight,
respectively). These subunits are derived from a 45kDa
proenzyme (p45) by way of a p30 form, through an
activation mechanism that is autocatalytic.
Thornberry, N.A. et al., Nature, 356, pp. 768-774
25 (1992). The ICE proenzyme has been divided into
several functional domains: a prodomain (p14), a
p22/20 subunit, a polypeptide linker and a p10 subunit.
Thornberry et al., supra; Casano et al., Genomics, 20,
pp. 474-481 (1994).

30 Full length p45 has been characterized by its
cDNA and amino acid sequences. PCT patent applications
WO 91/15577 and WO 94/00154. The p20 and p10 cDNA and
amino acid sequences are also known. Thornberry
et al., supra. Murine and rat ICE have also been
35 sequenced and cloned. They have high amino acid and

- 5 -

nucleic acid sequence homology to human ICE. Miller, D.K. et al., Ann. N.Y. Acad. Sci., 696, pp. 133-148 (1993); Molineaux, S.M. et al., Proc. Nat. Acad. Sci., 90, pp. 1809-1813 (1993). The three-dimensional structure of ICE has been determined at atomic resolution by X-ray crystallography. Wilson, K.P., et al., Nature, 370, pp. 270-275 (1994). The active enzyme exists as a tetramer of two p20 and two p10 subunits.

Additionally, there exist human homologs of ICE with sequence similarities in the active site regions of the enzymes. Such homologs include TX (or ICE_{rel-II} or ICH-2) (Faucheu, et al., EMBO J., 14, p. 1914 (1995); Kamens J., et al., J. Biol. Chem., 270, p. 15250 (1995); Nicholson et al., J. Biol. Chem., 270 15870 (1995)), TY (or ICE_{rel-III}) (Nicholson et al., J. Biol. Chem., 270, p. 15870 (1995); ICH-1 (or Nedd-2) (Wang, L. et al., Cell, 78, p. 739 (1994)), MCH-2, (Fernandes-Alnemri, T. et al., Cancer Res., 55, p. 2737 (1995), CPP32 (or YAMA or apopain) (Fernandes-Alnemri, T. et al., J. Biol. Chem., 269, p. 30761 (1994); Nicholson, D.W. et al., Nature, 376, p. 37 (1995)), and CMH-1 (or MCH-3) (Lippke, et al., J. Biol. Chem., (1996); Fernandes-Alnemri, T. et al., Cancer Res., (1995)). Each of these ICE homologs, as well as ICE itself, is capable of inducing apoptosis when overexpressed in transfected cell lines. Inhibition of one or more of these homologs with the peptidyl ICE inhibitor Tyr-Val-Ala-Asp-chloromethylketone results in inhibition of apoptosis in primary cells or cell lines. Lazebnik et al., Nature, 371, p. 346 (1994). The compounds described herein are also capable of inhibiting one or more homologs of ICE (see Example 5). Therefore, these compounds may be used to inhibit apoptosis in tissue types that contain ICE homologs, but which do not contain active ICE or produce mature

- 6 -

IL-1 β .

Interferon-gamma inducing factor (IGIF) is an approximately 18-kDa polypeptide that stimulates T-cell production of interferon-gamma (IFN- γ). IGIF is
5 produced by activated Kupffer cells and macrophages in vivo and is exported out of such cells upon endotoxin stimulation. Thus, a compound that decreases IGIF production would be useful as an inhibitor of such T-cell stimulation which in turn would reduce the levels
10 of IFN- γ production by those cells.

IFN- γ is a cytokine with immunomodulatory effects on a variety of immune cells. In particular, IFN- γ is involved in macrophage activation and Th1 cell selection (F. Belardelli, APMIS, 103, p. 161 (1995)).
15 IFN- γ exerts its effects in part by modulating the expression of genes through the STAT and IRF pathways (C. Schindler and J.E. Darnell, Ann. Rev. Biochem., 64, p. 621 (1995); T. Taniguchi, J. Cancer Res. Clin. Oncol., 121, p. 516 (1995)).

Mice lacking IFN- γ or its receptor have multiple defects in immune cell function and are resistant to endotoxic shock (S. Huang et al., Science, 259, p. 1742 (1993); D. Dalton et al., Science, 259, p. 1739 (1993); B. D. Car et al., J. Exp. Med., 179, p. 1437 (1994)). Along with IL-12, IGIF appears to be
25 a potent inducer of IFN- γ production by T cells (H. Okamura et al., Infection and Immunity, 63, p. 3966 (1995); H. Okamura et al., Nature, 378, p. 88 (1995); S. Ushio et al., J. Immunol., 156, p. 4274 (1996)).

30 IFN- γ has been shown to contribute to the pathology associated with a variety of inflammatory, infectious and autoimmune disorders and diseases. Thus, compounds capable of decreasing IFN- γ production

- 7 -

would be useful to ameliorate the effects of IFN- γ related pathologies.

5 The biological regulation of IGIF and thus IFN- γ has not been elucidated. It is known that IGIF is synthesized as a precursor protein, called "pro-IGIF". It has been unclear, however, how pro-IGIF is cleaved and whether its processing has biological importance.

10 Accordingly, compositions and methods capable of regulating the conversion of pro-IGIF to IGIF would be useful for decreasing IGIF and IFN- γ production in vivo, and thus for ameliorating the detrimental effects of these proteins which contribute to human disorders and diseases.

15 However, ICE and other members of the ICE/CED-3 family have not previously been linked to the conversion of pro-IGIF to IGIF or to IFN- γ production in vivo.

20 ICE inhibitors represent a class of compounds useful for the control of inflammation or apoptosis or both. Peptide and peptidyl inhibitors of ICE have been described. PCT patent applications WO 91/15577; WO 93/05071; WO 93/09135; WO 93/14777 and WO 93/16710; and European patent application 0 547 699. Such peptidyl
25 inhibitors of ICE has been observed to block the production of mature IL-1 β in a mouse model of inflammation (vide infra) and to suppress growth of leukemia cells *in vitro* (Estrov et al., Blood 84, 380a (1994)). However, due to their peptidic nature, such
30 inhibitors are typically characterized by undesirable pharmacologic properties, such as poor cellular penetration and cellular activity, poor oral absorption, poor stability and rapid metabolism. Plattner, J.J. and D.W. Norbeck, in Drug Discovery

- 8 -

Technologies, C.R. Clark and W.H. Moos, Eds. (Ellis Horwood, Chichester, England, 1990), pp. 92-126. This has hampered their development into effective drugs.

Non-peptidyl compounds have also been reported to inhibit ICE in vitro. PCT patent application WO 95/26958; US Patents 5,552,400; Dolle et al., J. Med. Chem., 39, pp. 2438-2440 (1996); However, it is not clear whether these compounds have the appropriate pharmacological profile to be therapeutically useful.

Additionally, current methods for the preparation of such compounds are not advantageous. These methods use tributyltin hydride, a toxic, moisture sensitive reagent. Thus, these methods are inconvenient to carry out, pose a health risk and create toxic-waste disposal problems. Furthermore, it is difficult to purify compounds prepared by these methods.

Accordingly, the need exists for compounds that can effectively inhibit the action of ICE *in vivo*, for use as agents for preventing and treating chronic and acute forms of IL-1-mediated diseases, apoptosis-, IGIF-, or IFN- γ -mediated diseases, as well as inflammatory, autoimmune, destructive bone, proliferative, infectious, or degenerative diseases. The need also exists for methods of preparing such compounds.

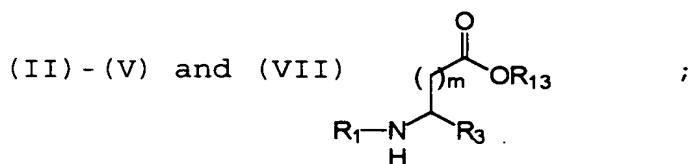
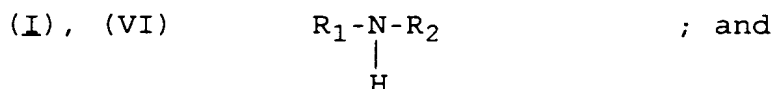
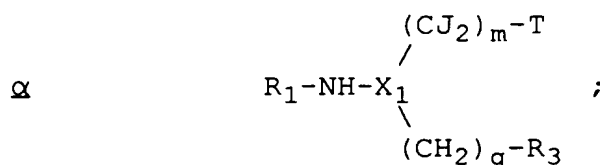
SUMMARY OF THE INVENTION

The present invention provides novel classes of compounds, and pharmaceutically acceptable derivatives thereof, that are useful as inhibitors of ICE. These compounds can be used alone or in combination with other therapeutic or prophylactic agents, such as antibiotics, immunomodulators or other anti-inflammatory agents, for the treatment or

- 9 -

prophylaxis of diseases mediated by IL-1, apoptosis, IGIF or IFN- γ . According to a preferred embodiment, the compounds of this invention are capable of binding to the active site of ICE and inhibiting the activity of that enzyme. Additionally, they have improved cellular potency, improved pharmacokinetics, and/or improved oral bioavailability compared to peptidyl ICE inhibitors.

It is a principal object of this invention to provide novel classes of compounds which are inhibitors of ICE represented by formulas:



wherein the various substituents are described herein.

It is a further object of this invention to provide a process of preparing N-acylamino compounds by coupling a carboxylic acid with an alloc-protected amine.

- 10 -

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1A ICE cleaves pro-IGIF in vivo. Cell lysates from Cos cells transfected with the various indicated expression plasmids or controls were analyzed for the presence of IGIF by separating proteins by SDS-PAGE and immunoblotting with anti-IGIF antisera (lane 1, mock transfected cells; lane 2, pro-IGIF alone; lanes 3-12, pro-IGIF in combination with ICE, ICE-C285S, CPP32, CPP32-C163S, CMH-1, CMH-1-C186S, Tx, Tx-C258S, respectively). Mobilities of pro-IGIF and the 18-kDa mature IGIF are indicated on the right. Molecular weight markers in kDa are shown on the left (Example 23).

Fig. 1B ICE cleaves pro-IGIF at the authentic processing site in vitro as shown by Coomassie blue staining of proteolytic reaction products separated by SDS-PAGE (Example 23). The proteases and inhibitors used were: lane 1, buffer control; lane 2, 0.1 nM ICE; lane 3, 1 nM ICE; lanes 4 and 5, 1 nM ICE with 10 nM Cbz-Val-Ala-Asp-[(2,6-dichlorobenzoyl)oxy]methyl ketone and 100 nM Ac-Tyr-Val-Ala-Asp-aldehyde, respectively; lanes 6 and 7, 15 nM CPP32 with and without 400 nM Ac-Asp-Glu-Val-Asp-aldehyde (D. W. Nicholson et al., Nature, 376, p. 37 (1995)), respectively; lane 8, 100 nM CMH-1; lane 9, 10 units/ml granzyme B; and M, molecular weight markers in kDa.

Fig. 1C ICE cleavage converts inactive pro-IGIF to active IGIF which induces IFN- γ production in Th1 helper cells. Uncleaved (Pro-IGIF), ICE-cleaved (Pro-IGIF/ICE), CPP32-cleaved (Pro-IGIF/ CPP32), and recombinant mature IGIF (rIGIF) were incubated with

- 11 -

A.E7 Th1 cells at 12 ng/ml (open bar) and 120 ng/ml (hatched bar) for eighteen hours and the levels of IFN- γ released into the culture medium assayed by ELISA (Example 23). A.E7 cells cultured with buffer, ICE alone (ICE) or CPP32 alone (CPP32) were assayed similarly for negative controls. The numbers represent the average of three determinations.

Fig. 2A Mature IGIF (18-kDa) is produced by Cos cells co-transfected with pro-IGIF and ICE-expressing plasmids. Cell lysates (left) and conditioned medium (right) from Cos cells transfected with a pro-IGIF expression plasmid in the absence (-) or presence of an expression plasmid encoding wild type (ICE) or inactive mutant (ICE-C285S) ICE. Transfected cells were metabolically labeled with ^{35}S -methionine, proteins from cell lysates and conditioned medium immunoprecipitated with anti-IGIF antisera and separated by SDS-PAGE (Example 24). Mobilities of pro-IGIF and the 18-kDa mature IGIF are indicated on the right. Molecular weight markers in kDa are shown on the left.

Fig. 2B IFN- γ inducing activity is detected in Cos cells co-transfected with pro-IGIF and ICE-expressing plasmids. Cell lysates (hatched bar) and conditioned medium (open bar) from Cos cells transfected with a pro-IGIF expression plasmid in the absence (Pro-IGIF) or presence (Pro-IGIF/ICE) of an expression plasmid encoding wild type (ICE) were assayed for IFN- γ levels (ng/ml) by ELISA. Cos cells transfected with buffer (Mock) or an ICE-expressing plasmid alone (ICE) served as negative controls (Example 24).

- 12 -

Fig. 3A Kupffer cells from mice lacking ICE are defective in the export of IGIF. Kupffer cells from wild type mice (ICE +/+) or ICE-deficient mice homozygous for an ICE mutation (ICE -/-) were isolated and primed with LPS for three hours. The levels of immunoreactive IGIF polypeptides in the conditioned media (ng/ml) of wild type cells were measured by ELISA (Example 25). N.D. (not detectable) indicates that the IGIF concentration was less than 0.1 ng/ml.

Fig. 3B Kupffer cells from mice lacking ICE are defective in the export of mature IGIF. Kupffer cells from wild type mice (ICE +/+) or ICE deficient mice homozygous for an ICE mutation (ICE -/-) were isolated and primed with LPS for three hours. Primed cells were metabolically labeled with ³⁵S-methionine, proteins from cell lysates and conditioned medium immunoprecipitated with anti-IGIF antisera and separated by SDS-PAGE (Example 25). Mobilities of pro-IGIF and the 18-kDa mature IGIF are indicated on the right. Molecular mass markers in kDa are shown on the left.

Fig. 3C Serum from ICE-deficient mice contains reduced levels of IGIF. Serum samples from wild type mice (ICE +/+) or ICE deficient mice homozygous for an ICE mutation (ICE -/-) were assayed for IGIF levels (ng/ml) by ELISA (Example 25).

Fig. 3D Serum from ICE-deficient mice contains reduced levels of IFN- γ . Serum samples from wild type mice (ICE +/+) or ICE deficient mice homozygous for an ICE mutation (ICE -/-) were assayed for IFN- γ levels (ng/ml) by ELISA (Example 25).

- 13 -

Fig. 4 Serum IFN- γ levels are significantly reduced in ICE-deficient mice after an acute challenge with LPS (Example 26). Serum samples from wild type mice (filled squares) or ICE-deficient mice (filled circles) were assayed for IFN- γ levels (ng/ml) by ELISA as a function of time (hours) after LPS challenge. Temperatures of the animals during the time course in degrees Celcius is shown for wild type mice (open squares) or ICE-deficient mice (open circles).

Fig. 5 The ICE inhibitor, AcYVAD-aldehyde (AcYVAD-CHO), inhibits LPS-stimulated IL-1 β and IFN- γ synthesis by human peripheral blood mononuclear cells (PBMC). Percent (%) inhibition as a function of inhibitor concentration (μ M) is shown for IL-1 β (open squares) and IFN- γ (open diamonds) synthesis.

Fig. 6 Compound **214e** inhibits IL-1 β production in LPS-challenged mice. Serum samples from CD1 mice were assayed for IL-1 β levels (pg/ml) by ELISA after LPS challenge. Compound **214e** was administered by intraperitoneal (IP) injection one hour after LPS challenge. Blood was collected seven hours after LPS challenge (see Example 7).

Fig. 7 Compound **217e** inhibits IL-1 β production in LPS-challenged mice. Serum samples from CD1 mice were assayed for IL-1 β levels (pg/ml) by ELISA after LPS challenge. Compound **217e** was administered by intraperitoneal (IP) injection one hour after LPS challenge. Blood was collected seven hours after LPS challenge (see Example 7).

Fig. 8 Compound **214e**, but not compound **217e**,

- 14 -

inhibits IL-1 β production in LPS-challenged mice when administered by oral gavage. This assay measures oral absorption under similar conditions as those described for Figs. 6 and 7. These results indicates that **214e** is potentially orally active as an ICE inhibitor (see Example 7).

Fig. 9 Compound **214e** and analogs of **214e** also inhibit IL-1 β production after IP administration. These results were obtained in the assay described for **Figs. 6 and 7** and Example 7.

Fig. 10 Compound **214e**, and analogs of **214e**, also inhibit IL-1 β production after oral (PO) administration. These results were obtained in the assay described for **Figs. 6 and 7** and Example 7.

Fig. 11 Compounds **302** and **304a** show detectable blood levels when administered orally (50mg/kg, in 0.5 % carboxymethylcellulose) to mice. Blood samples were collected at 1 and 7 hours after dosing. Compounds **302** and **304a** are prodrugs of **214e** and are metabolized to **214e in vivo**. Compound **214e** shows no blood levels above 0.10 μ g/ml when administered orally (Example 8).

Fig. 12 Compound **412f** blocks the progression of type II collagen-induced arthritis in male DBA/1J mice (Wooley, P.H., Methods in Enzymology, 162, pp. 361-373 (1988) and Geiger, T., Clinical and Experimental Rheumatology, 11, pp. 515-522 (1993)). Compound **412f** was administered twice a day (10, 25 and 50mg/kg), approximately 7h apart, by oral gavage. Inflammation was measured on the Arthritis Severity Score on a 1 to 4 scale of increasing severity. The scores of the two front paws were added to give the final score (see Example 21).

- 15 -

Fig. 13 Compound **412d** blocks the progression of type II collagen-induced arthritis in male DBA/1J mice. The results were obtained as described for **Fig. 12** and in Example 21.

5 **Fig. 14** Compound **696a** blocks the progression of type II collagen-induced arthritis in male DBA/1J mice. The results were obtained as described for **Fig. 12** and in Example 21.

ABBREVIATIONS AND DEFINITIONS

10

Abbreviations

<u>Designation</u>	<u>Reagent or Fragment</u>
Ala	alanine
Arg	arginine
Asn	asparagine
15 Asp	aspartic acid
Cys	cysteine
Gln	glutamine
Glu	glutamic acid
Gly	glycine
20 His	histidine
Ile	isoleucine
Leu	leucine
Lys	lysine
Met	methionine
25 Phe	phenylalanine
Pro	proline
Ser	serine
Thr	threonine
Trp	tryptophan
30 Tyr	tyrosine
Val	valine
Ac ₂ O	acetic anhydride
n-Bu	normal-butyl

- 16 -

	DMF	dimethylformamide
	DIEA	<i>N,N</i> -diisopropylethylamine
	EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
5	Et ₂ O	diethyl ether
	EtOAc	ethyl acetate
	Fmoc	9-fluorenylmethoxycarbonyl
	HBTU	O-benzotriazol-1-yl- <i>N,N,N',N'</i> -tetramethyluronium
10		hexafluorophosphate
	HOBT	1-hydroxybenzotriazole hydrate
	MeOH	methanol
	TFA	trifluoroacetic acid
15	Alloc	allyloxycarbonyl

Definitions

The following terms are employed herein:

The term "interferon gamma inducing factor" or "IGIF" refers to a factor which is capable of stimulating the endogenous production of IFN- γ .

The term "ICE inhibitor" refers to a compound which is capable of inhibiting the ICE enzyme. ICE inhibition may be determined using the methods described and incorporated by reference herein. The skilled practitioner realizes that an in vivo ICE inhibitor is not necessarily an in vitro ICE inhibitor. For example, a prodrug form of a compound typically demonstrates little or no activity in in vitro assays. Such prodrug forms may be altered by metabolic or other biochemical processes in the patient to provide an in vivo ICE inhibitor.

The term "cytokine" refers to a molecule which mediates interactions between cells.

The term "condition" refers to any disease,

- 17 -

disorder or effect that produces deleterious biological consequences in a subject.

5 The term "subject" refers to an animal, or to one or more cells derived from an animal. Preferably, the animal is a mammal, most preferably a human. Cells may be in any form, including but not limited to cells retained in tissue, cell clusters, immortalized cells, transfected or transformed cells, and cells derived from an animal that have been physically or
10 phenotypically altered.

 The term "active site" refers to any or all of the following sites in ICE: the substrate binding site, the site where an inhibitor binds and the site where the cleavage of substrate occurs.

15 The term "heterocycle" or "heterocyclic" refers to a stable mono- or polycyclic compound which may optionally contain one or two double bonds or may optionally contain one or more aromatic rings. Each heterocycle consists of carbon atoms and from one to
20 four heteroatoms independently selected from a group including nitrogen, oxygen, and sulfur. As used herein, the terms "nitrogen heteroatoms" and "sulphur heteroatoms" include any oxidized form of nitrogen or sulfur and the quaternized form of any basic nitrogen.
25 Heterocycles defined above include, for example, pyrimidinyl, tetrahydroquinolyl, tetrahydroisoquinolyl, purinyl, pyrimidyl, indolyl, benzimidazolyl, imidazolyl, imidazolinoyl, imidazolidinyl, quinolyl, isoquinolyl, indolyl,
30 pyridyl, pyrrolyl, pyrrolinyl, pyrazolyl, pyrazinyl, quinoxolyl, piperidinyl, morpholinyl, thiamorpholinyl, furyl, thienyl, triazolyl, thiazolyl, β -carbolinyl, tetrazolyl, thiazolidinyl, benzofuranoyl, thiamorpholinyl sulfone, benzoxazolyl, oxopiperidinyl,
35 oxopyrroldinyl, oxoazepinyl, azepinyl, isoxazolyl,

Sub
A2

- 18 -

Sub
A2

tetrahydropyranyl, tetrahydrofuranyl, thiadiazolyl, benzodioxolyl, benzothienyl, tetrahydrothiophenyl and sulfolanyl. Further heterocycles are described in A.R. Katritzky and C.W. Rees, eds., Comprehensive Heterocyclic Chemistry: The Structure, Reactions, Synthesis and Use of Heterocyclic Compounds, Vol. 1-8, Pergamon Press, NY (1984).

The term "cycloalkyl" refers to a mono- or polycyclic group which contains 3 to 15 carbons and may optionally contain one or two double bonds. Examples include cyclohexyl, adamantyl and norbornyl.

The term "aryl" refers to a mono- or polycyclic group which contains 6, 10, 12, or 14 carbons in which at least one ring is aromatic. Examples include phenyl, naphthyl, and tetrahydronaphthalene.

The term "heteroaromatic" refers to a mono- or polycyclic group which contains 1 to 15 carbon atoms and from 1 to 4 heteroatoms, each of which is selected independently from a group including sulphur, nitrogen and oxygen, and which additionally contains from 1 to 3 five or six membered rings, at least one of which is aromatic.

The term "alpha-amino acid" (α -amino acid) refers to both the naturally occurring amino acids and other "non-protein" α -amino acids commonly utilized by those in the peptide chemistry arts when preparing synthetic analogues of naturally occurring peptides, including D and L forms. The naturally occurring amino acids are glycine, alanine, valine, leucine, iso-leucine, serine, methionine, threonine, phenylalanine, tyrosine, tryptophan, cysteine, proline, histidine, aspartic acid, asparagine, glutamic acid, glutamine, γ -carboxyglutamic acid, arginine, ornithine and lysine. Examples of "non-protein" alpha-amino acids include

- 19 -

hydroxylysine, homoserine, homotyrosine, homo-phenylalanine, citrulline, kynurenine, 4-amino-phenylalanine, 3-(2-naphthyl)-alanine, 3-(1-naphthyl)-alanine, methionine sulfone, t-butyl-alanine, 5 t-butylglycine, 4-hydroxyphenylglycine, aminoalanine, phenylglycine, vinylalanine, propargyl-glycine, 1,2,4-triazolo-3-alanine, 4,4,4-trifluoro-threonine, thyronine, 6-hydroxytryptophan, 5-hydroxytryptophan, 3-hydroxykynurenine, 3-aminotyrosine, trifluoromethyl-10 alanine, 2-thienylalanine, (2-(4-pyridyl)ethyl)-cysteine, 3,4-dimethoxy-phenylalanine, 3-(2-thiazolyl)-alanine, ibotenic acid, 1-amino-1-cyclopentane-carboxylic acid, 1-amino-1-cyclohexanecarboxylic acid, quisqualic acid, 3-trifluoromethylphenylalanine, 15 4-trifluoro-methylphenylalanine, cyclohexylalanine, cyclo-hexylglycine, thiohistidine, 3-methoxytyrosine, elastatinal, norleucine, norvaline, alloisoleucine, homoarginine, thioproline, dehydroproline, hydroxyproline, isonipectotic acid, homoproline, cyclohexyl-20 glycine, α -amino-n-butyric acid, cyclohexylalanine, aminophenylbutyric acid, phenylalanines substituted at the ortho, meta, or para position of the phenyl moiety with one or two of the following: a (C_1 - C_4) alkyl, a (C_1 - C_4) alkoxy, halogen or nitro groups or substituted 25 with a methylenedioxy group; β -2- and 3-thienyl-alanine, β -2- and 3-furanylalanine, β -2-, 3- and 4-pyridylalanine, β -(benzothienyl-2- and 3-yl)alanine, β -(1- and 2-naphthyl)alanine, O-alkylated derivatives of serine, threonine or tyrosine, S-alkylated cysteine, 30 S-alkylated homocysteine, O-sulfate, O-phosphate and O-carboxylate esters of tyrosine, 3-sulfo-tyrosine, 3-carboxy-tyrosine, 3-phospho-tyrosine, 4-methane sulfonic acid ester of tyrosine, 4-methane phosphonic acid ester of tyrosine, 3,5-diiodotyrosine, 3-nitro-35 tyrosine, ϵ -alkyl lysine, and delta-alkyl ornithine.

- 20 -

Any of these α -amino acids may be substituted with a methyl group at the alpha position, a halogen at any aromatic residue on the α -amino side chain, or an appropriate protective group at the O, N, or S atoms of the side chain residues. Appropriate protective groups are disclosed in "Protective Groups In Organic Synthesis," T.W. Greene and P.G.M. Wuts, J. Wiley & Sons, NY, NY, 1991.

The term "substitute" refers to the replacement of a hydrogen atom in a compound with a substituent group. In the present invention, those hydrogen atoms which form a part of a hydrogen bonding moiety which is capable of forming a hydrogen bond with the carbonyl oxygen of Arg-341 of ICE or the carbonyl oxygen of Ser-339 of ICE are excluded from substitution. These excluded hydrogen atoms include those which comprise an -NH- group which is alpha to a -CO- group and are depicted as -NH- rather than an X group or some other designation in the following diagrams: (a) through (t), (v) through (z).

The term "straight chain" refers to a contiguous unbranching string of covalently bound atoms. The straight chain may be substituted, but these substituents are not a part of the straight chain.

The term " K_i " refers to a numerical measure of the effectiveness of a compound in inhibiting the activity of a target enzyme such as ICE. Lower values of K_i reflect higher effectiveness. The K_i value is a derived by fitting experimentally determined rate data to standard enzyme kinetic equations (see I. H. Segel, Enzyme Kinetics, Wiley-Interscience, 1975).

The term "patient" as used in this application refers to any mammal, especially humans.

The term "pharmaceutically effective amount" refers to an amount effective in treating or

- 21 -

ameliorating an IL-1-, apoptosis-, IGIF- or IFN- γ - mediated disease in a patient. The term "prophylactically effective amount" refers to an amount effective in preventing or substantially lessening

5 IL-1-, apoptosis-, IGIF or IFN- γ mediated diseases in a patient.

The term "pharmaceutically acceptable carrier or adjuvant" refers to a non-toxic carrier or adjuvant that may be administered to a patient, together with a

10 compound of this invention, and which does not destroy the pharmacological activity thereof.

The term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, or salt of such ester, of a compound of this

15 invention or any other compound which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention or an anti-ICE active metabolite or residue thereof.

Pharmaceutically acceptable salts of the

20 compounds of this invention include, for example, those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic,

25 lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable,

30 may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal (e.g., sodium), alkaline earth

35 metal (e.g., magnesium), ammonium and N-(C₁₋₄ alkyl)₄⁺

- 22 -

salts.

This invention also envisions the "quaternization" of any basic nitrogen-containing groups of the compounds disclosed herein. The basic nitrogen can be quaternized with any agents known to those of ordinary skill in the art including, for example, lower alkyl halides, such as methyl, ethyl, propyl and butyl chloride, bromides and iodides; dialkyl sulfates including dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aralkyl halides including benzyl and phenethyl bromides. Water or oil-soluble or dispersible products may be obtained by such quaternization.

The ICE inhibitors of this invention may contain one or more "asymmetric" carbon atoms and thus may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be of the R or S configuration. Although specific compounds and scaffolds exemplified in this application may be depicted in a particular stereochemical configuration, compounds and scaffolds having either the opposite stereochemistry at any given chiral center or mixtures thereof are also envisioned.

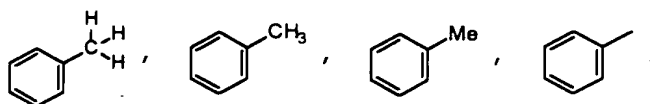
The ICE inhibitors of this invention may comprise ring structures which may optionally be substituted at carbon, nitrogen or other atoms by various substituents. Such ring structures may be singly or multiply substituted. Preferably, the ring structures contain between 0 and 3 substituents. When multiply substituted, each substituent may be picked independently of any other substituent as long as the

- 23 -

combination of substituents results in the formation of a stable compound.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and administration to a mammal by methods known in the art. Typically, such compounds are stable at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

Substituents may be represented in various forms. These various forms are known to the skilled practitioner and may be used interchangeably. For example, a methyl substituent on a phenyl ring may be represented in any of the following forms:



Various forms of substituents such as methyl are used herein interchangeably.

20 DETAILED DESCRIPTION OF THE INVENTION

In order that the invention herein described may be more fully understood, the following detailed description is set forth.

The ICE inhibitors of one embodiment (A) of this invention are those of formula α :



wherein:

- 24 -

X_1 is -CH;

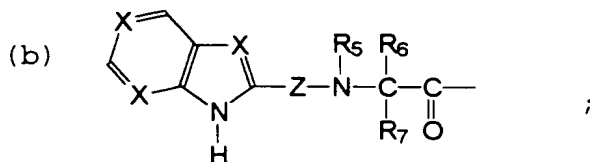
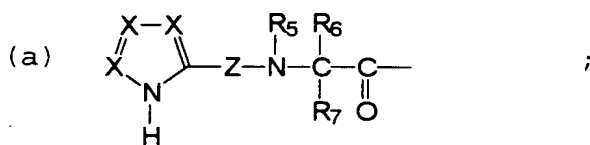
g is 0 or 1;

each J is independently selected from the group consisting of -H, -OH, and -F, provided that when a first and second J are bound to a C and said first J is -OH, said second J is -H;

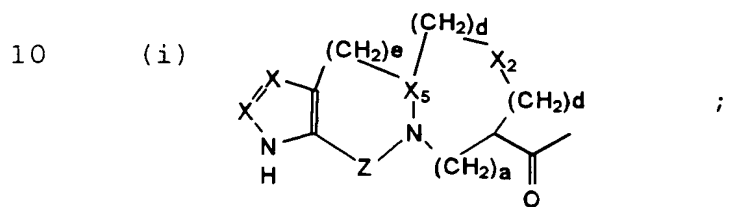
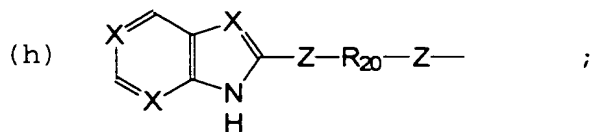
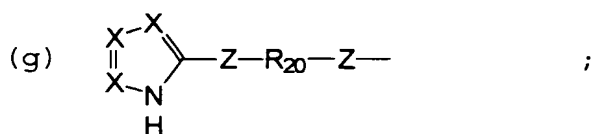
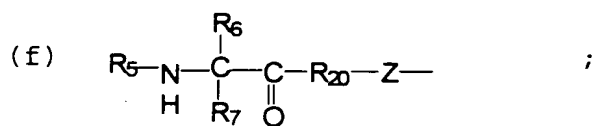
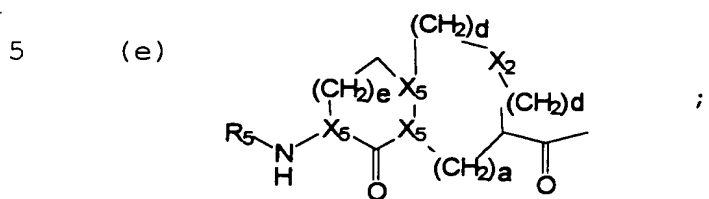
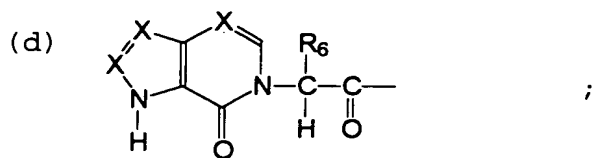
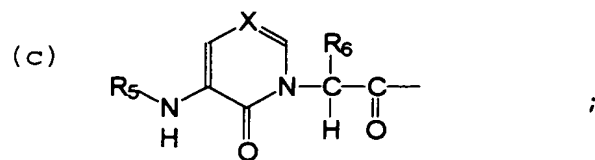
m is 0, 1, or 2;

T is -OH, -CO-CO₂H, -CO₂H, or any bioisosteric replacement for -CO₂H;

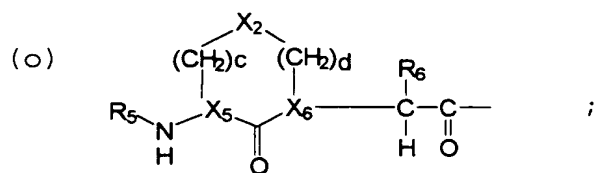
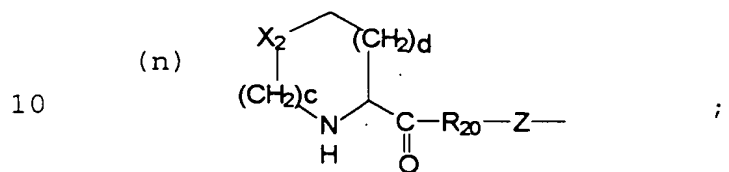
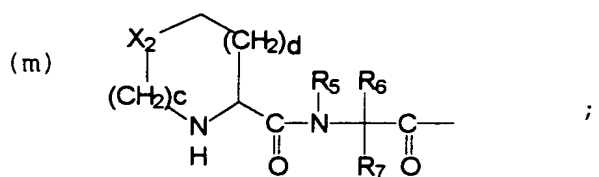
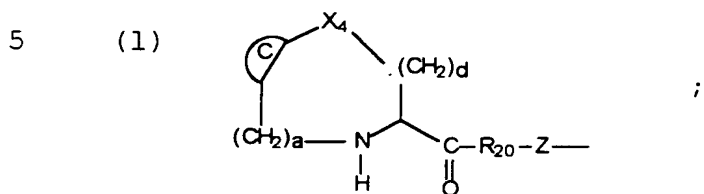
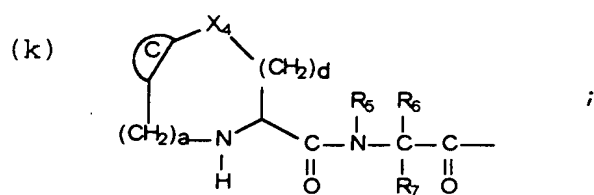
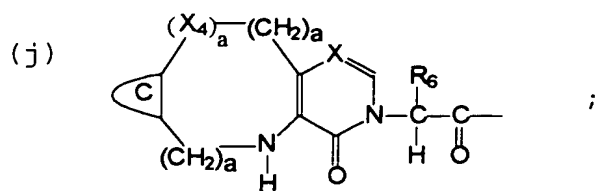
R_1 is selected from the group consisting of the following formulae, in which any ring may optionally be singly or multiply substituted at any carbon by Q_1 , at any nitrogen by R_5 , or at any atom by =O, -OH, -CO₂H, or halogen; any saturated ring may optionally be unsaturated at one or two bonds; and wherein R_1 (e) and R_1 (y) are optionally benzofused;



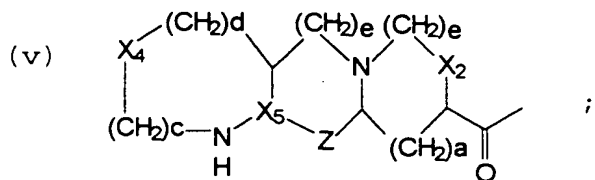
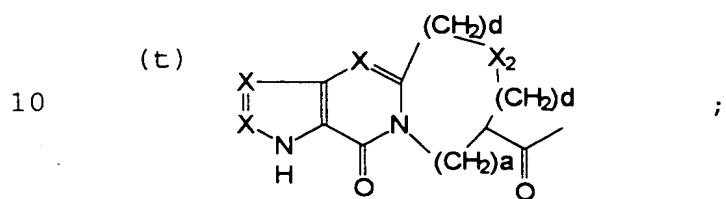
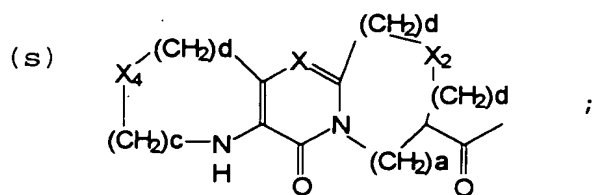
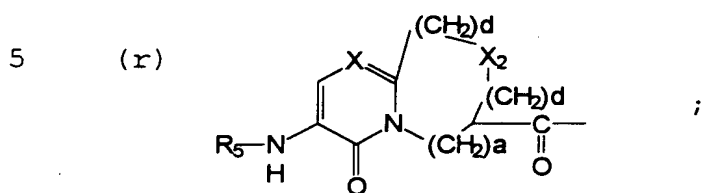
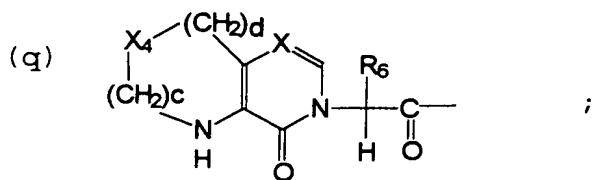
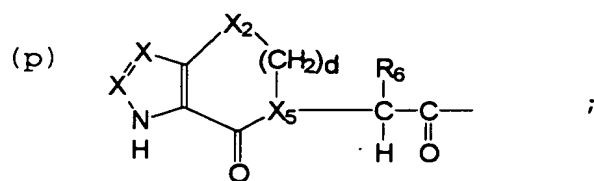
- 25 -



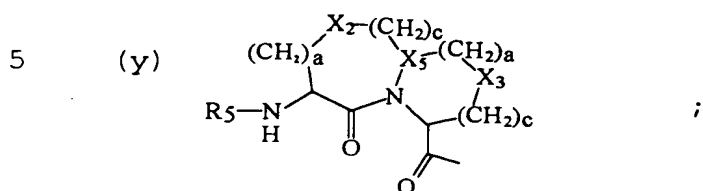
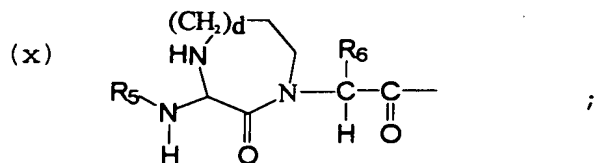
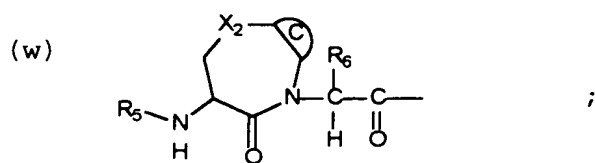
- 26 -



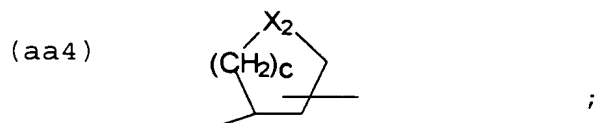
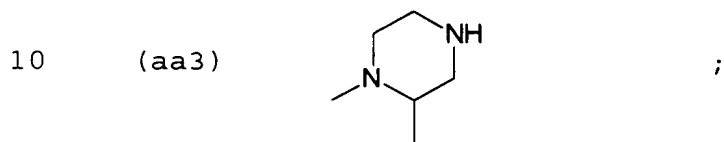
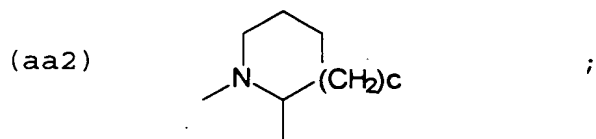
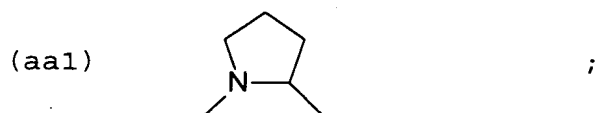
- 27 -



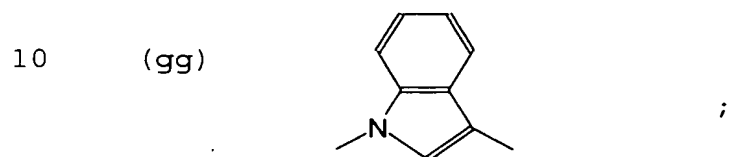
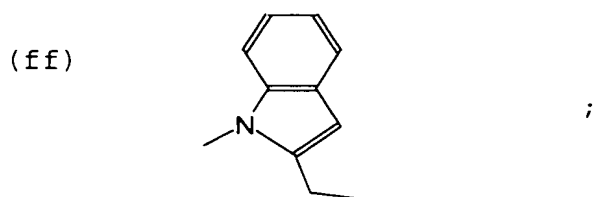
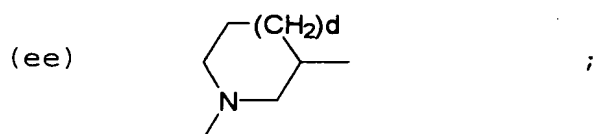
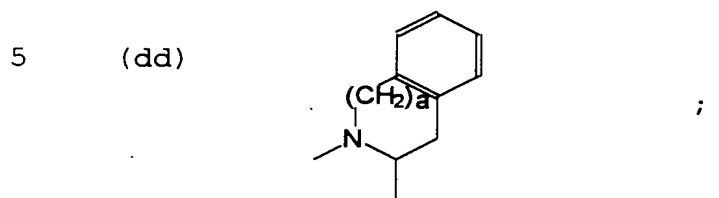
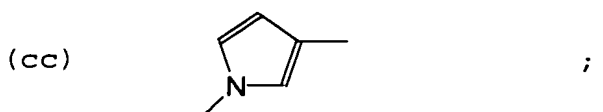
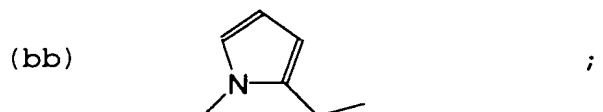
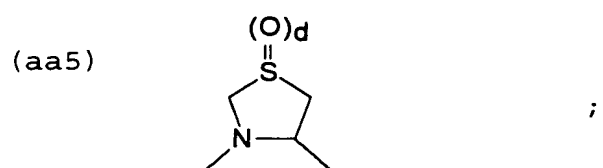
- 28 -



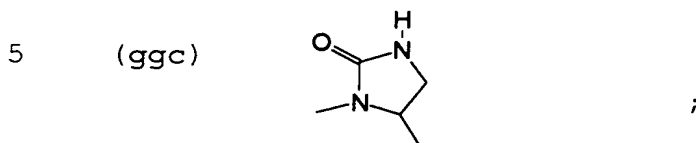
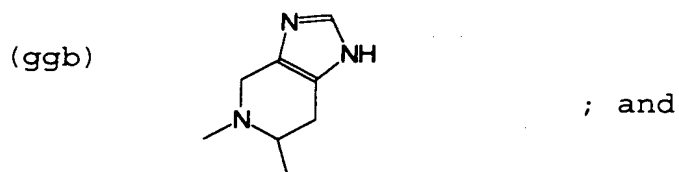
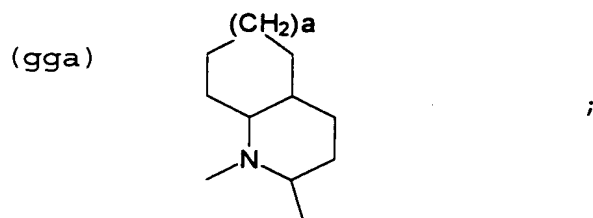
R₂₀ is selected from the group consisting of:



- 29 -



- 30 -



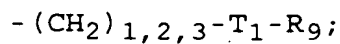
wherein each ring C is independently chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo,
 10 pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

R_3 is:
 -CN,
 -CH=CH- R_9 ,
 -CH=N-O- R_9 ,
 15 - $(CH_2)_{1-3}$ - T_1 - R_9 ,
 -CJ₂- R_9 ,
 -CO- R_{13} , or
 -CO-CO-N $\begin{matrix} /R_5 \\ \backslash R_{10} \end{matrix}$;
 20

each R_4 is independently selected from the group consisting of:

-H,
 -Ar₁,
 25 - R_9 ,
 - T_1 - R_9 , and

- 31 -



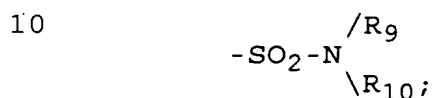
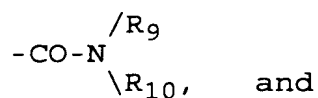
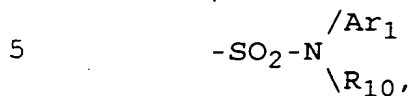
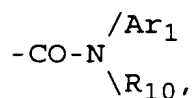
each T_1 is independently selected from the group consisting of:

- CH=CH-,
- 5 -O-,
- S-,
- SO-,
- SO₂-,
- NR₁₀-,
- 10 -NR₁₀-CO-,
- CO-,
- O-CO-,
- CO-O-,
- CO-NR₁₀-,
- 15 -O-CO-NR₁₀-,
- NR₁₀-CO-O-,
- NR₁₀-CO-NR₁₀-,
- SO₂-NR₁₀-,
- NR₁₀-SO₂-, and
- 20 -NR₁₀-SO₂-NR₁₀-;

each R_5 is independently selected from the group consisting of:

- H,
- Ar₁,
- 25 -CO-Ar₁,
- SO₂-Ar₁,
- CO-NH₂,
- SO₂-NH₂,
- R₉,
- 30 -CO-R₉,
- CO-O-R₉,
- SO₂-R₉,

- 32 -



15 R_6 and R_7 taken together form a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-; or R_7 is -H and R_6 is

-H

-Ar₁,

-R₉,

- (CH₂)_{1,2,3}-T₁-R₉, or

20 an α-amino acid side chain residue;

each R_9 is a C₁₋₆ straight or branched alkyl group optionally singly or multiply substituted with -OH, -F, or =O and optionally substituted with one or two Ar₁ groups;

25 each R_{10} is independently selected from the group consisting of -H or a C₁₋₆ straight or branched alkyl group;

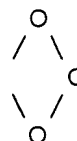
each R_{13} is independently selected from the group consisting of -Ar₂, -R₄ and -N-OH

30 \backslash
R₅;

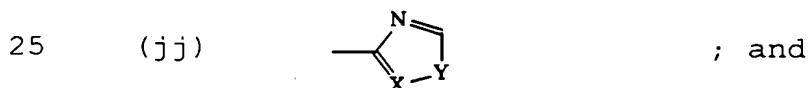
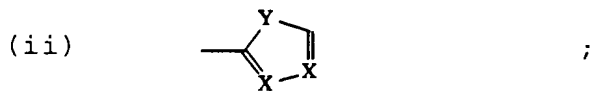
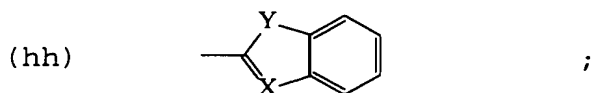
each Ar₁ is a cyclic group independently selected

- 33 -

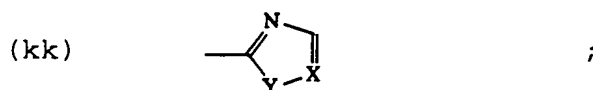
from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3 rings, said cycloalkyl group being optionally benzofused, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocycle group containing at least one heteroatom group selected from -O-, -S-, -SO-, -SO₂-, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted with -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN,

=O, -OH, -perfluoro C₁₋₃ alkyl, CH₂, or -Q₁;

each Ar₂ is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q₁ and -Q₂:



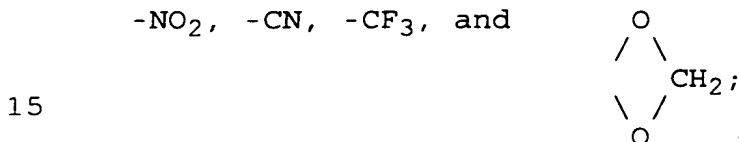
- 34 -



each Q_1 is independently selected from the group consisting of:

- 5 $-Ar_1$
 $-O-Ar_1$
 $-R_9$,
 $-T_1-R_9$, and
 $-(CH_2)_{1,2,3}-T_1-R_9$;

10 each Q_2 is independently selected from the group consisting of $-OH$, $-NH_2$, $-CO_2H$, $-Cl$, $-F$, $-Br$, $-I$, $-NO_2$, $-CN$, $-CF_3$, and



provided that when $-Ar_1$ is substituted with a Q_1 group which comprises one or more additional $-Ar_1$ groups, said additional $-Ar_1$ groups are not substituted with Q_1 ;

20

each X is independently selected from the group consisting of $=N-$, and $=CH-$;

each X_2 is independently selected from the group consisting of $-O-$, $-CH_2-$, $-NH-$, $-S-$, $-SO-$, and $-SO_2-$;

25 each X_3 is independently selected from the group consisting of $-CH_2-$, $-S-$, $-SO-$, and $-SO_2-$;

each X_4 is independently selected from the group consisting of $-CH_2-$ and $-NH-$;

- 35 -

each X_5 is independently selected from the group
 consisting of $\begin{array}{c} -CH- \\ | \end{array}$ and $\begin{array}{c} -N- \\ | \end{array}$;

X_6 is $-CH-$ or $-N-$;

5 each Y is independently selected from the group
 consisting of $-O-$, $-S-$, and $-NH$;

each Z is independently CO or SO_2 ;

each a is independently 0 or 1;

each c is independently 1 or 2;

10 each d is independently 0, 1, or 2; and

each e is independently 0, 1, 2, or 3;

provided that when

R_1 is (f),

15 R_6 is an α -amino acid side chain residue, and

R_7 is $-H$,

then (aa1) and (aa2) must be substituted with Q_1 ;

also provided that when

20 R_1 is (o),

g is 0,

J is $-H$,

m is 1,

R_6 is an α -amino acid side chain residue,

25 R_7 is $-H$,

X_2 is $-CH_2-$,

X_5 is $\begin{array}{c} -CH- \\ | \end{array}$,

30 X_6 is $\begin{array}{c} -N- \\ | \end{array}$, and

R_3 is $\begin{array}{c} /R_{10} \\ -CO-N \\ \backslash R_{10} \end{array}$, or $-CO-R_{13}$, when

- 36 -

R_{13} is:

- 5 -CH₂-O-CO-Ar₁,
 -CH₂-S-CO-Ar₁,
 -CH₂-O-Ar₁,
 -CH₂-S-Ar₁, or
 -R₄ when -R₄ is -H;

then the ring of the R₁(o) group must be substituted with Q₁ or benzofused; and

provided that when

- 10 R₁ is (w),
 g is 0,
 J is -H,
 m is 1,
 T is -CO₂H,
 15 X₂ is O,
 R₅ is benzyloxycarbonyl, and
 ring C is benzo,

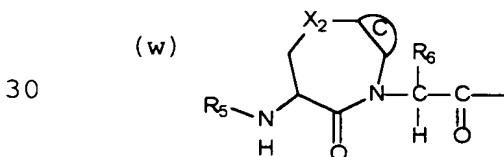
then R₃ cannot be -CO-R₁₃ when:

- R₁₃ is -CH₂-O-Ar₁ and
 20 Ar₁ is 1-phenyl-3-trifluoromethyl-
 pyrazole-5-yl wherein the phenyl is optionally
 substituted with a chlorine atom;

or when

- R₁₃ is -CH₂-O-CO-Ar₁, wherein
 25 Ar₁ is 2,6-dichlorophenyl.

Preferred compounds of embodiment A employ formula α , wherein R₁ is (w):

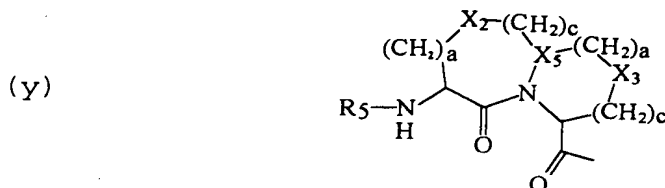


wherein the other substituents are as described

- 37 -

above.

Other preferred compounds of embodiment A employ formula α , wherein R_1 is (y):



5 wherein the other substituents are as described above.

More preferred compounds of embodiment A employ formula α , wherein:

X_1 is -CH;

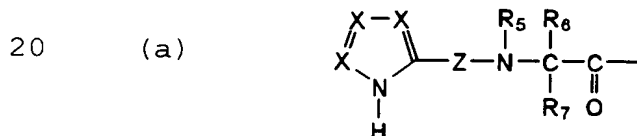
10 g is 0;

J is -H;

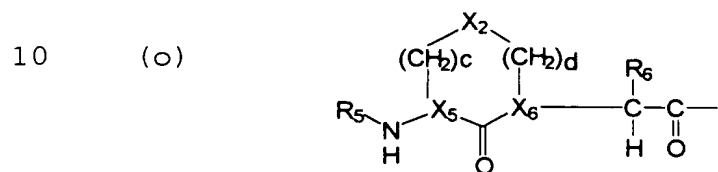
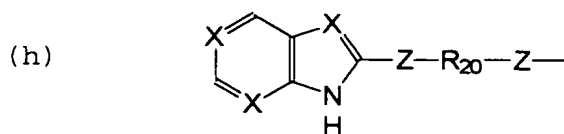
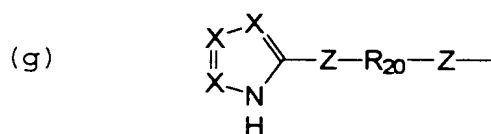
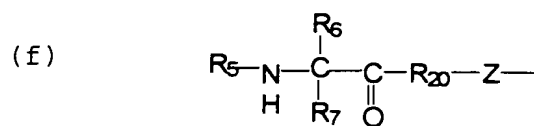
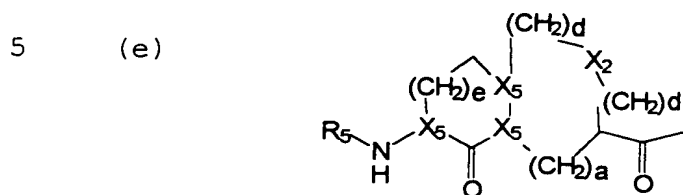
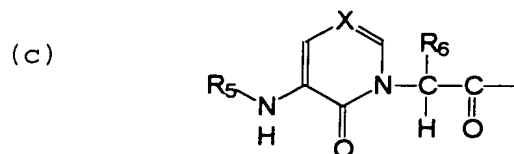
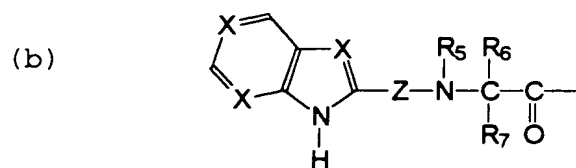
m is 0 or 1 and T is -CO-CO₂H, or any bioisosteric replacement for -CO₂H, or

m is 1 and T is -CO₂H;

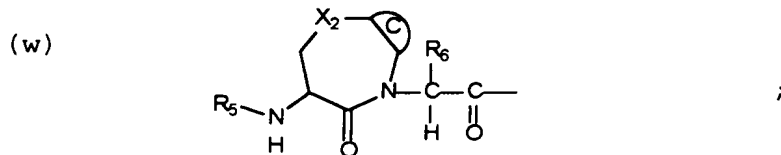
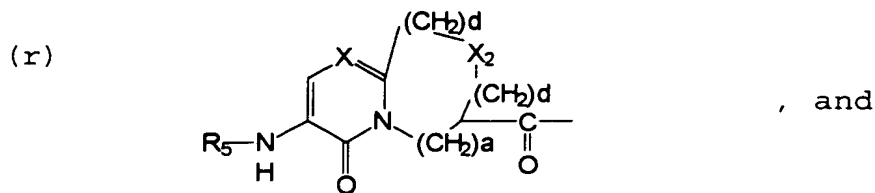
15 R_1 is selected from the group consisting of the following formulae, in which any ring may optionally be singly or multiply substituted at any carbon by Q_1 , at any nitrogen by R_5 , or at any atom by =O, -OH, -CO₂H, or halogen, and wherein (e) is optionally benzofused:



- 38 -

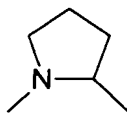


- 39 -

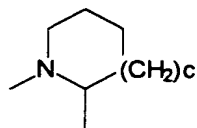


5 R_{20} is:

(aa1)



(aa2)



and c is 1;

10 ring C is benzo optionally substituted with
-C₁₋₃ alkyl, -O-C₁₋₃ alkyl, -Cl, -F or -CF₃;

when R₁ is (a) or (b), R₅ is preferably -H, and

15 when R₁ is (c), (e), (f), (o), (r), (w), (x) or
(y), R₅ is preferably:

-CO-Ar₁
-SO₂-Ar₁,
-CO-NH₂,
-CO-NH-Ar₁
20 -CO-R₉,
-CO-O-R₉,

- 40 -

-SO₂-R₉, or-CO-NH-R₉,R₇ is -H and R₆ is: -H,-R₉, or

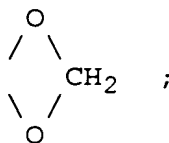
5

-Ar₁;

R₉ is a C₁₋₆ straight or branched alkyl group optionally substituted with =O and optionally substituted with -Ar₁;

10 R₁₀ is -H or a -C₁₋₃ straight or branched alkyl group;

Ar₁ is phenyl, naphthyl, pyridyl, benzothiazolyl, thienyl, benzothienyl, benzoxazolyl, 2-indanyl, or indolyl optionally substituted with -O-C₁₋₃ alkyl, -NH-C₁₋₃ alkyl, -N-(C₁₋₃ alkyl)₂, -Cl, -F, -CF₃,
15 -C₁₋₃ alkyl, or



20 Q₁ is R₉ or -(CH₂)_{0,1,2}-T₁-(CH₂)_{0,1,2}-Ar₁, wherein T₁ is -O- or -S-;

each X is independently selected from the group consisting of =N-, and =CH-;

25 each X₂ is independently selected from the group consisting of -O-, -CH₂-, -NH-, -S-, -SO-, and -SO₂-;

each X₅ is independently selected from the group consisting of -CH- and -N-;

30 X₆ is -CH- or -N-,
| |

- 41 -

provided that when:

R_1 is (o),

X_2 is $-\text{CH}_2-$,

5 X_5 is $-\text{CH}-$, and
 $\quad \quad \quad |$

X_6 is $-\text{N}-$,
 $\quad \quad \quad |$

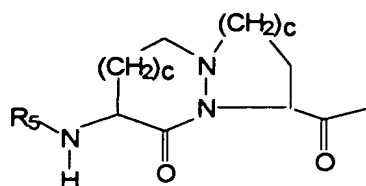
10 then the ring of the $R_1(o)$ group must be
substituted with Q_1 or benzofused; and

Z is $\text{C}=\text{O}$.

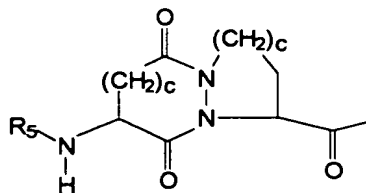
Most preferably, compounds of this more
preferred embodiment are those wherein the R_1 group is:

(e1)

15

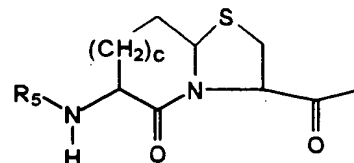


(e2)

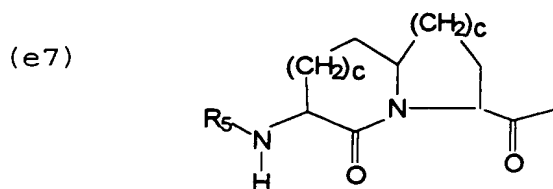


and c is 2; or

(e4)



- 42 -



which is optionally benzofused,
and c is 1 or 2;

provided that when R₁ is (e4),

5 g is 0,
 J is -H,
 m is 1,
 T is -CO₂H,
 R₅ is benzyloxycarbonyl, and
10 c is 1,

then R₃ cannot be -CO-R₁₃ when

R₁₃ is -CH₂-O-Ar₁ and

Ar₁ is 1-phenyl-3-trifluoromethyl-pyrazole-
5-yl, wherein the phenyl is optionally substituted with
15 a chlorine atom; or when

R₁₃ is -CH₂-O-CO-Ar₁, wherein

Ar₁ is 2,6-dichlorophenyl,

and when the 2-position of the scaffold ring is
20 substituted with para-fluoro-phenyl; and

also provided that when

R₁ is (e7),
g is 0,
J is -H,
25 m is 1,
T is -CO₂H or -CO-NH-OH,
R₅ is a protective group for the N atom of an
amino acid side chain residue, and
each c is 1,

- 43 -

then R_3 cannot be $-\text{CO}-R_{13}$ when

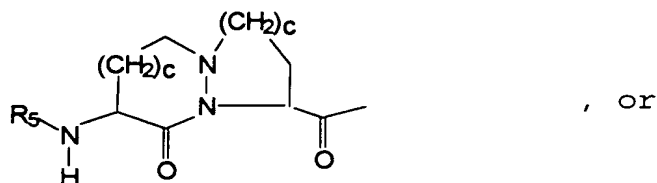
R_{13} is:

- 5
- $-\text{CH}_2-\text{O}-\text{CO}-\text{Ar}_1,$
 - $-\text{CH}_2-\text{S}-\text{CO}-\text{Ar}_1,$
 - $-\text{CH}_2-\text{O}-\text{Ar}_1,$ or
 - $-\text{CH}_2-\text{S}-\text{Ar}_1.$

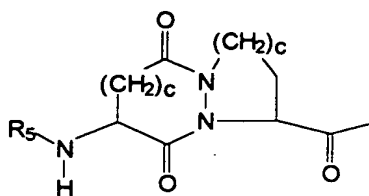
The most preferred compounds of this embodiment are those wherein:

R_1 is:

10 (e1)



(e2)



and c is 2;

m is 1;

15 T is $-\text{CO}_2\text{H}$; and

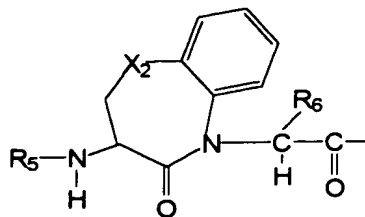
R_3 is $-\text{CO}-R_{13}.$

Other most preferred compounds of this embodiment are those wherein:

R_1 is:

- 44 -

(w1)



; wherein

X₂ is:

-O- ,
 -S- ,
 -SO₂-, or
 -NH-;

5

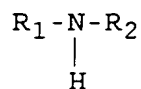
optionally substituted with R₅ or Q₁ at X₂ when X₂
 10 is -NH-; and

ring C is benzo substituted with -C₁₋₃ alkyl,
 -O-C₁₋₃ alkyl, -Cl, -F or -CF₃.

The ICE inhibitors of another embodiment (B)
 of this invention are those of formula (I):

15

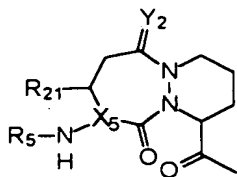
(I)



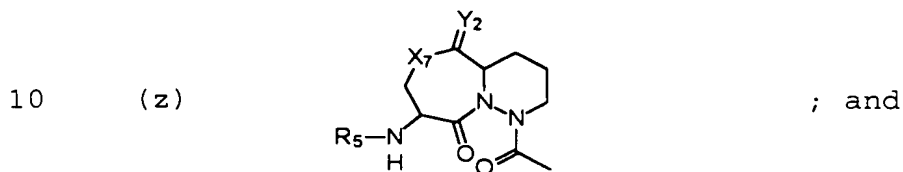
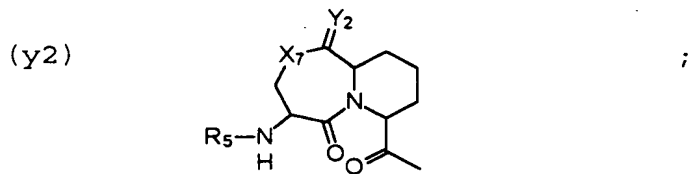
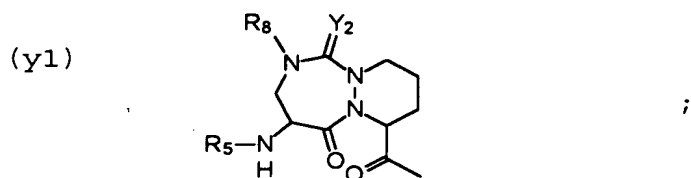
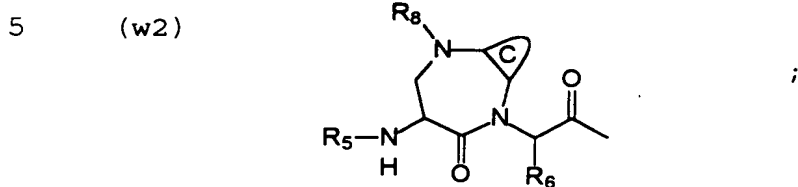
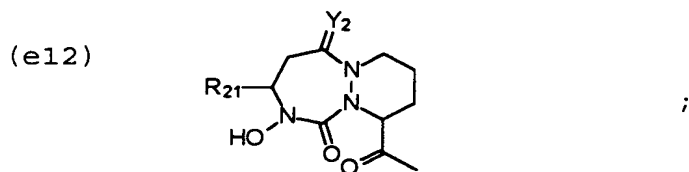
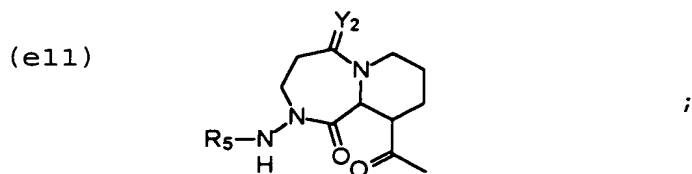
wherein:

R₁ is selected from the group consisting of the
 20 following formulae:

(e10)



- 45 -

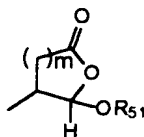


ring C is chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

- 46 -

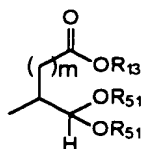
 R_2 is:

(a)



, or

(b)



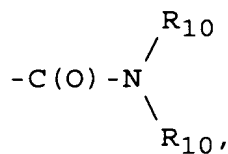
;

 m is 1 or 2;

5

 R_5 is selected from the group consisting of: $-C(O)-R_{10}$, $-C(O)O-R_9$,

10

 $-S(O)_2-R_9$,

15

 $-C(O)-CH_2-O-R_9$, $-C(O)C(O)-R_{10}$, $-R_9$, $-H$, and $-C(O)C(O)-OR_{10}$;

20

 X_5 is $-CH-$ or $-N-$; Y_2 is H_2 or O ; X_7 is $-N(R_8)-$ or $-O-$;

25

- 47 -

R_6 is selected from the group consisting of -H and -CH₃;

R_8 is selected from the group consisting of:

- 5 -C(O)-R₁₀,
 -C(O)O-R₉,
 -C(O)-N(H)-R₁₀,
 -S(O)₂-R₉,
 -S(O)₂-NH-R₁₀,
10 -C(O)-CH₂-OR₁₀,
 -C(O)C(O)-R₁₀;
 -C(O)-CH₂N(R₁₀)(R₁₀),
 -C(O)-CH₂C(O)-O-R₉,
 -C(O)-CH₂C(O)-R₉,
15 -H, and
 -C(O)-C(O)-OR₁₀;

each R₉ is independently selected from the group consisting of -Ar₃ and a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein
20 the -C₁₋₆ alkyl group is optionally unsaturated;

each R₁₀ is independently selected from the group consisting of -H, -Ar₃, a C₃₋₆ cycloalkyl group, and a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein the -C₁₋₆ alkyl group is
25 optionally unsaturated;

R₁₃ is selected from the group consisting of H, Ar₃, and a C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, -CONH₂, -OR₅, -OH, -OR₉, or -CO₂H;

- 48 -

each R_{51} is independently selected from the group consisting of R_9 , $-C(O)-R_9$, $-C(O)-N(H)-R_9$, or each R_{51} taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing $-O-$, $-S-$, or $-NH-$;

5 each R_{21} is independently selected from the group consisting of $-H$ or a $-C_{1-6}$ straight or branched alkyl group;

10 each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from $-O-$, $-S-$, $-SO-$, SO_2 , $=N-$, and $-NH-$,
15 said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

20 each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, $-Cl$, $-F$, $-Br$, $-I$, $-NO_2$, $-CN$, $=O$, $-OH$, $-perfluoro\ C_{1-3}\ alkyl$, R_5 , $-OR_5$, $-NHR_5$, OR_9 , $-NHR_9$, R_9 , $-C(O)-R_{10}$, and



30 provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

- 49 -

Preferably, R_5 is selected from the group consisting of:

- 5 - $C(O)-R_{10}$,
 - $C(O)O-R_9$, and
 - $C(O)-NH-R_{10}$.

Alternatively, R_5 is selected from the group consisting of:

- 10 - $S(O)_2-R_9$,
 - $S(O)_2-NH-R_{10}$,
 - $C(O)-C(O)-R_{10}$,
 - R_9 , and
 - $C(O)-C(O)-OR_{10}$.

More preferably:

m is 1;

- 15 R_{13} is H or a $-C_{1-4}$ straight or branched alkyl group optionally substituted with $-Ar_3$, $-OH$, $-OR_9$, or $-CO_2H$, wherein the R_9 is a $-C_{1-4}$ branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1 ;

- 20 R_{21} is $-H$ or $-CH_3$;

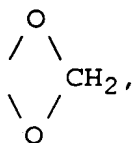
R_{51} is a C_{1-6} straight or branched alkyl group optionally substituted with Ar_3 , wherein Ar_3 is phenyl, optionally substituted by $-Q_1$;

- 25 Ar_3 is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl benzofuranyl, and indolyl;

- 50 -

each Q_1 is independently selected from the group consisting of $-NH_2$, $-Cl$, $-F$, $-Br$, $-OH$, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

5



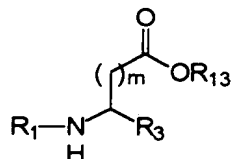
10 wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

15 provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

The ICE inhibitors of another embodiment (C) of this invention are those of formula (II):

20

(II)



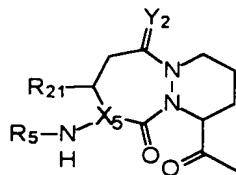
wherein:

m is 1 or 2;

R_1 is selected from the group consisting of the following formulae:

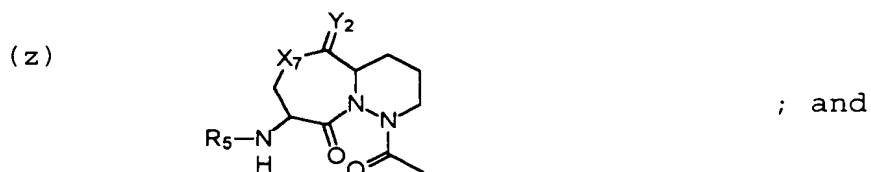
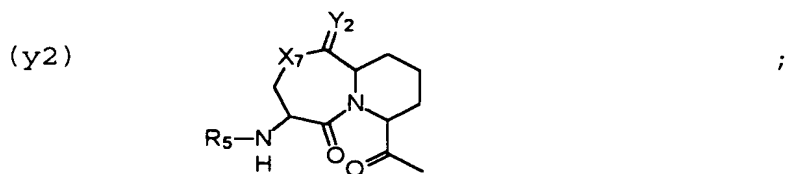
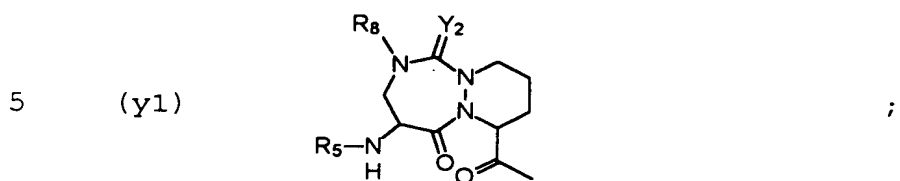
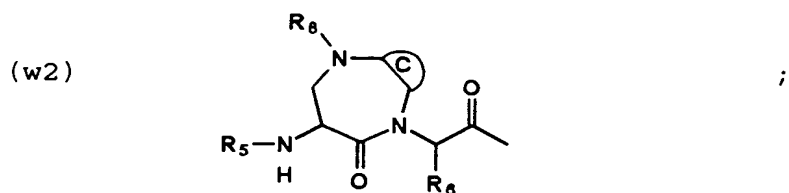
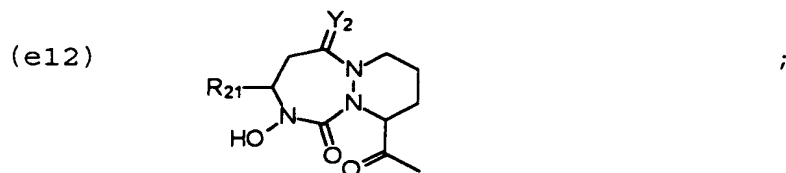
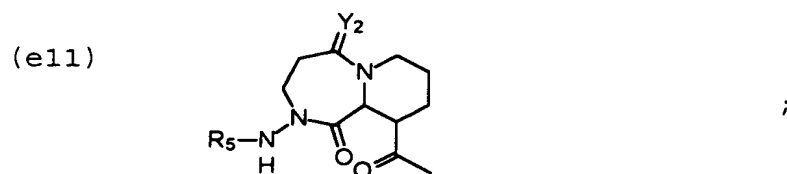
25

(e10)



;

- 51 -



10 ring C is chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

- 52 -

R_3 is selected from the group consisting of:

- CN,
- C(O)-H,
- C(O)-CH₂-T₁-R₁₁,
- 5 -C(O)-CH₂-F,
- C=N-O-R₉, and
- CO-Ar₂;

R_5 is selected from the group consisting of:

- C(O)-R₁₀,
- 10 -C(O)O-R₉,
-
- 15
$$\begin{array}{c} R_{10} \\ \diagup \\ -C(O)-N \\ \diagdown \\ R_{10} \end{array},$$
- S(O)₂-R₉,
- C(O)-CH₂-O-R₉,
- C(O)C(O)-R₁₀,
- 20 -R₉,
- H, and
- C(O)C(O)-OR₁₀,

25 X_5 is $\begin{array}{c} -CH- \\ | \end{array}$ or $\begin{array}{c} -N- \\ | \end{array}$;

Y_2 is H₂ or O;

X_7 is -N(R₈)- or -O-;

30 each T₁ is independently selected from the group consisting of -O-, -S-, -S(O)-, and -S(O)₂-;

R_6 is selected from the group consisting of -H and -CH₃;

R_8 is selected from the group consisting of:

- 53 -

5
 -C(O)-R₁₀,
 -C(O)O-R₉,
 -C(O)-NH-R₁₀,
 -S(O)₂-R₉,
 -S(O)₂-NH-R₁₀,
 -C(O)-CH₂-OR₁₀,
 -C(O)C(O)-R₁₀,
 -C(O)-CH₂-N(R₁₀)(R₁₀),
 -C(O)-CH₂C(O)-O-R₉,
 10 -C(O)-CH₂C(O)-R₉,
 -H, and
 -C(O)-C(O)-OR₁₀;

15 each R₉ is independently selected from the group consisting of -Ar₃ and a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein the -C₁₋₆ alkyl group is optionally unsaturated;

20 each R₁₀ is independently selected from the group consisting of -H, -Ar₃, a C₃₋₆ cycloalkyl group, and a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein the -C₁₋₆ alkyl group is optionally unsaturated;

each R₁₁ is independently selected from the group consisting of:

25 -Ar₄,
 -(CH₂)₁₋₃-Ar₄,
 -H, and
 -C(O)-Ar₄;

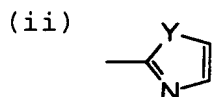
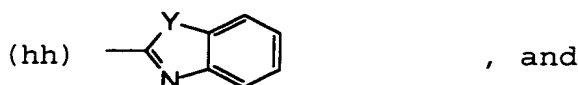
30 R₁₃ is selected from the group consisting of H, Ar₃, and a C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, -CONH₂, -OR₅, -OH, -OR₉, or -CO₂H;

- 54 -

-OR₁₃ is optionally -N(H)-OH;

each R₂₁ is independently selected from the group consisting of -H or a -C₁₋₆ straight or branched alkyl group;

5 Ar₂ is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q₁:



10

wherein each Y is independently selected from the group consisting of O and S;

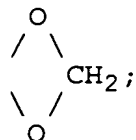
each Ar₃ is a cyclic group independently selected from the set consisting of an aryl group which contains
 15 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO₂, =N-, and -NH-,
 20 -N(R₅)-, and -N(R₉)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q₁;

25 each Ar₄ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and

- 55 -

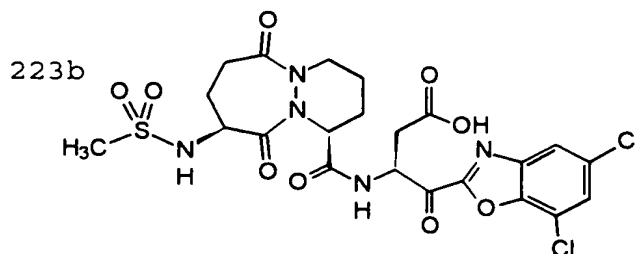
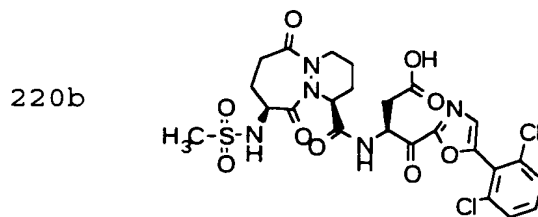
15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO₂, =N-, -NH-, -N(R₅)-, and -N(R₉)- said heterocycle group optionally
 5 containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q₁;

each Q₁ is independently selected from the group
 10 consisting of -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH, -perfluoro C₁₋₃ alkyl, R₅, -OR₅, -NHR₅, OR₉, -NHR₉, R₉, -C(O)-R₁₀, and



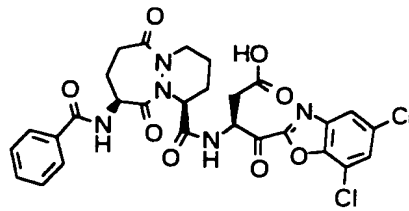
provided that when -Ar₃ is substituted with a Q₁
 20 group which comprises one or more additional -Ar₃ with another -Ar₃.

Preferred compounds of this embodiment include, but are not limited to:

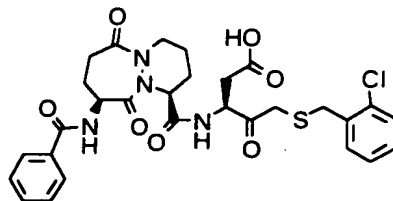


- 56 -

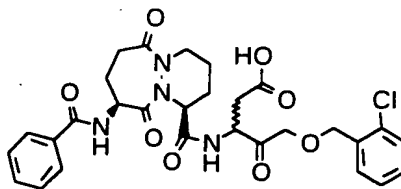
223e



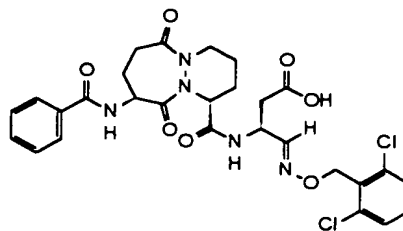
226e



227e

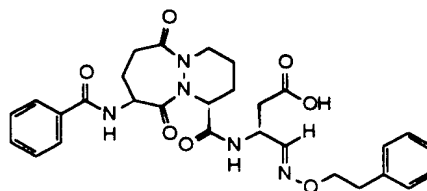


307a



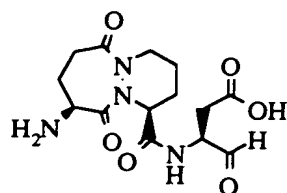
5

307b

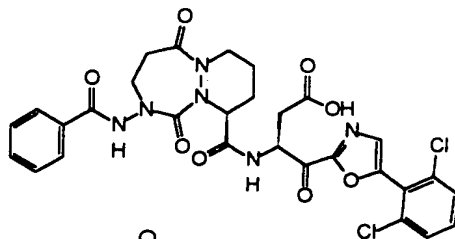


- 57 -

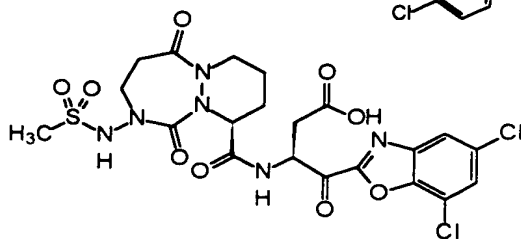
429



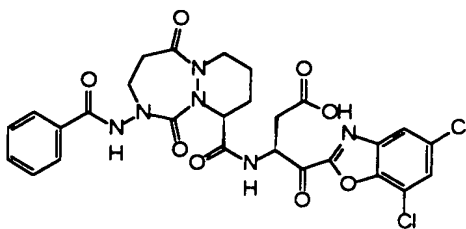
820b



823b

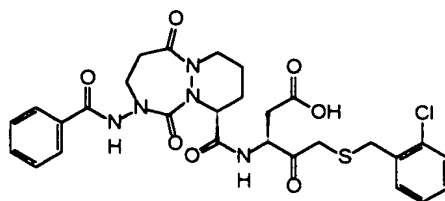


823e

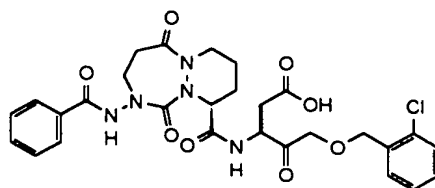


5

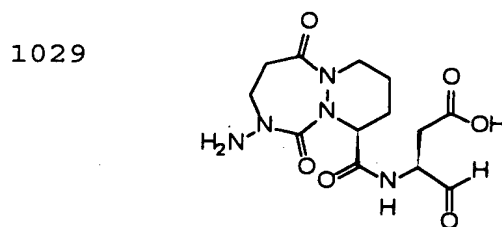
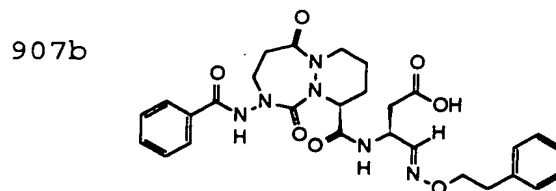
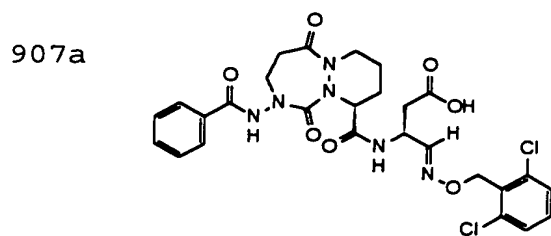
826e



827e



- 58 -



5 Preferred compounds of embodiment C employ formula (II), wherein R_1 is (e11) and the other substituents are as defined above.

Other preferred compounds of embodiment C employ formula (II), wherein R_1 is (e12) and the other substituents are as defined above.

10 Other preferred compounds of embodiment C employ formula (II) wherein R_1 is (y1) and the other substituents are as defined above.

15 Other preferred compounds of embodiment C employ formula (II) wherein R_1 is (y2) and the other substituents are as defined above.

- 59 -

Other preferred compounds of embodiment C of employ formula (II) wherein R_1 is (z) and the other substituents are as defined above.

5 Other preferred compound of embodiment C employ formula (II) wherein R_1 is (w2) and the other substituents are as defined above.

More preferably, R_1 is (w2) and

m is 1;

ring C is benzo, pyrido, or thieno;

10 R_3 is selected from the group consisting of -C(O)-H, -C(O)-Ar₂, and -C(O)CH₂-T₁-R₁₁;

R_5 is selected from the group consisting of:

-C(O)-R₁₀, wherein R_{10} is -Ar₃;

-C(O)O-R₉, wherein R_9 is -CH₂-Ar₃;

15 -C(O)C(O)-R₁₀, wherein R_{10} is -CH₂Ar₃;

-R₉, wherein R_9 is a C₁₋₂ alkyl group substituted with -Ar₃; and

-C(O)C(O)-OR₁₀, wherein R_{10} is -CH₂Ar₃;

20 T₁ is O or S;

R₆ is H;

R₈ is selected from the group consisting -C(O)-R₁₀, -C(O)-CH₂-OR₁₀, and -C(O)CH₂-N(R₁₀)(R₁₀), wherein R_{10} is H, CH₃, or -CH₂CH₃;

25 R_{11} is selected from the group consisting of -Ar₄, -(CH₂)₁₋₃-Ar₄, and -C(O)-Ar₄;

- 60 -

R_{13} is H or a $-C_{1-4}$ straight or branched alkyl group optionally substituted with $-Ar_3$, $-OH$, $-OR_9$, or $-CO_2H$, wherein the R_9 is a $-C_{1-4}$ branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1 ;

Ar_2 is (hh);

Y is O;

Ar_3 is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl;

Ar_4 is phenyl, tetrazolyl, naphthyl, pyridinyl, oxazolyl, pyrimidinyl, or indolyl;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-Cl$, $-F$, $-Br$, $-OH$, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and



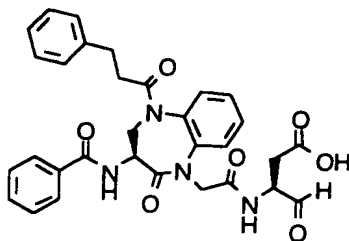
wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

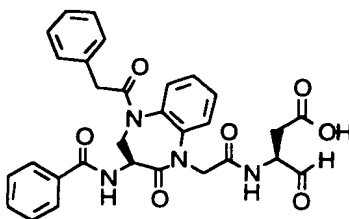
- 61 -

Preferred compounds of this embodiment include, but are not limited to:

605a

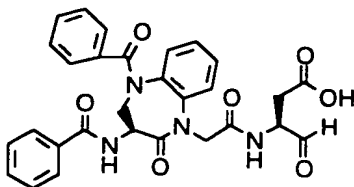


605b

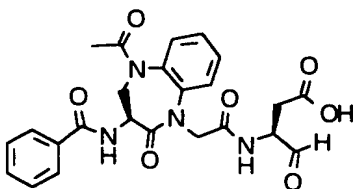


5

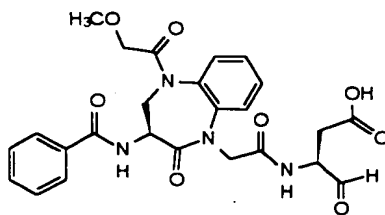
605c



605d

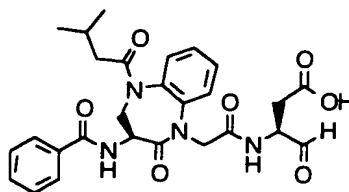


605e

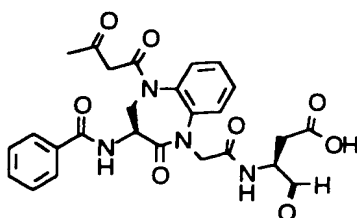


- 62 -

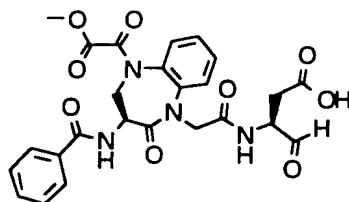
605f



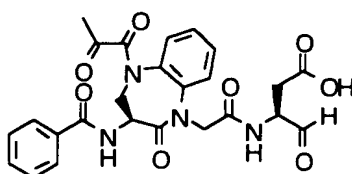
605g



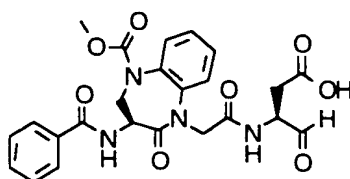
605h



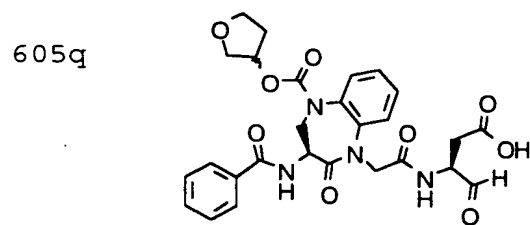
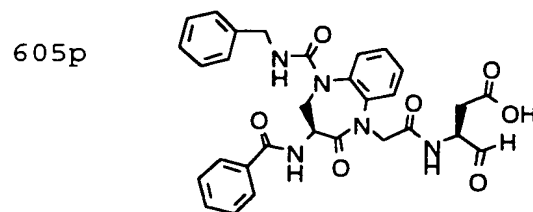
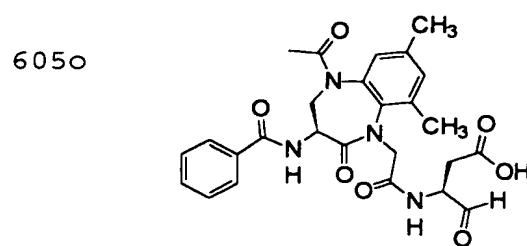
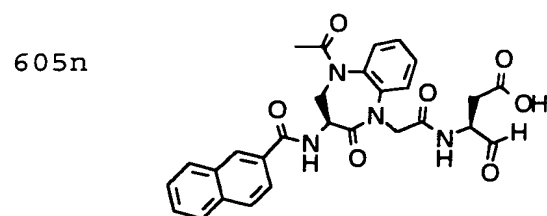
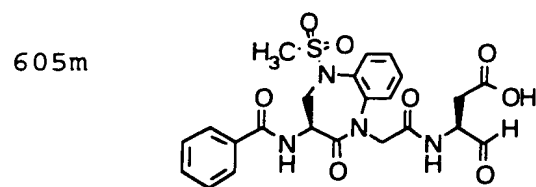
605i



605j

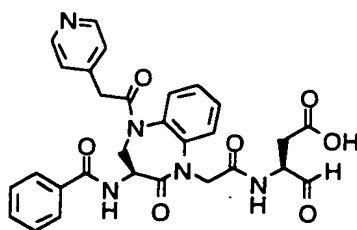


- 63 -

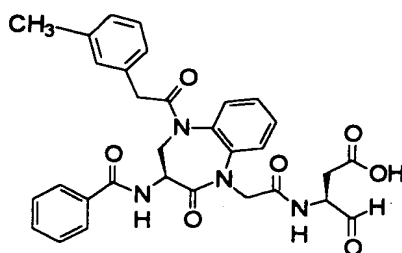


- 64 -

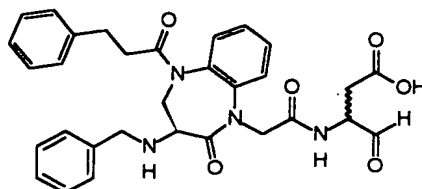
605s



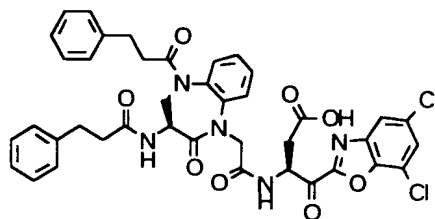
605t



605v

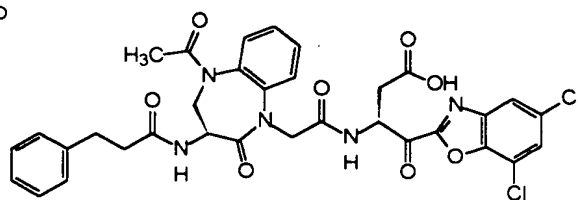


609a



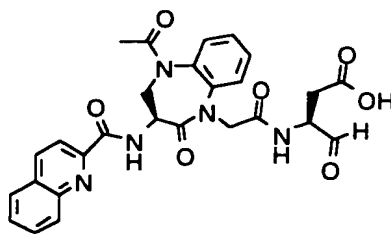
5

609b

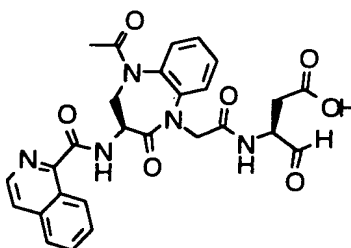


- 65 -

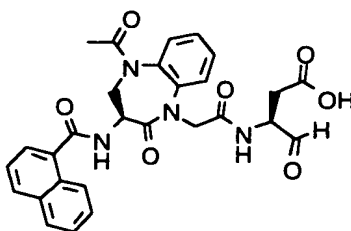
619



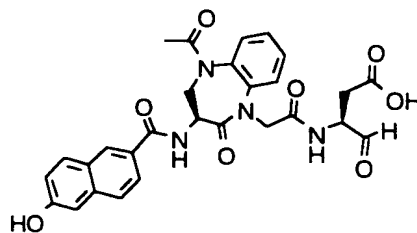
620



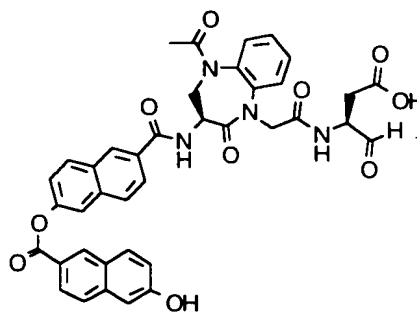
621



622

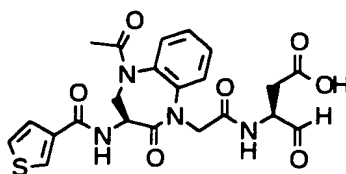


623

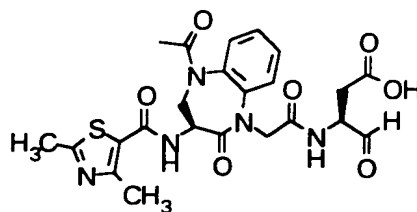


- 66 -

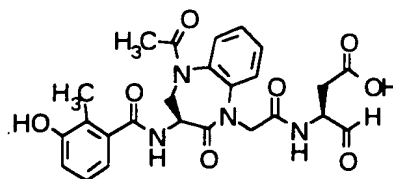
624



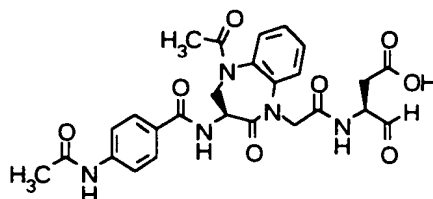
625



626

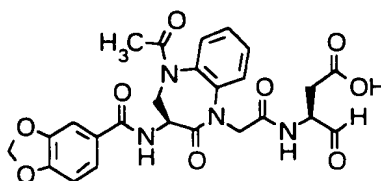


627



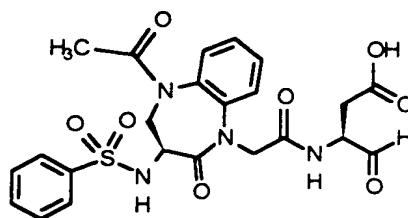
5

628

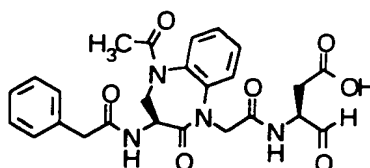


- 67 -

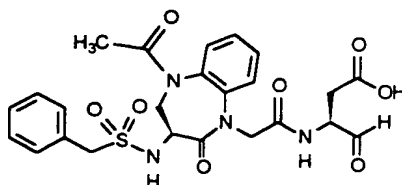
629



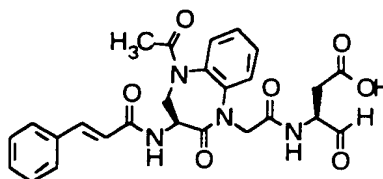
630



631

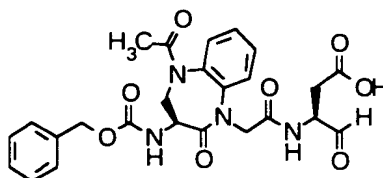


632

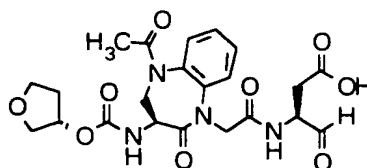


5

633

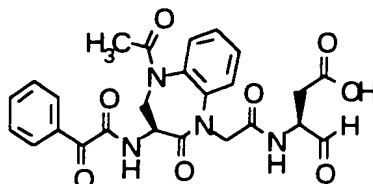


634



- 68 -

635



Other preferred compounds of embodiment C
employ formula (II) wherein R_1 is (e10), X_5 is CH, and
the other substituents are as defined above.

More preferred compounds of embodiment C
employ formula (II) wherein R_1 is (e10), X_5 is CH, R_3 is
 CO-Ar_2 , and the other substituents are as defined
above.

Other more preferred compounds of embodiment
C employ formula (II) wherein R_1 is (e10), X_5 is CH, R_3
is $-\text{C(O)}-\text{CH}_2-\text{T}_1-\text{R}_{11}$, R_{11} is $-(\text{CH}_2)_{1-3}-\text{Ar}_4$, and the other
substituents are as defined above.

Other more preferred compounds of embodiment
C employ formula (II) wherein R_1 is (e10) and X_5 is CH
and

R_3 is $-\text{C(O)}-\text{CH}_2-\text{T}_1-\text{R}_{11}$;

T_1 is O; and

R_{11} is $-\text{C(O)}-\text{Ar}_4$,

and the other substituents are as defined above.

More preferably, in these more preferred compounds, R_5
is selected from the group consisting of:

$-\text{C(O)}-\text{R}_{10}$,

$-\text{C(O)}\text{O}-\text{R}_9$, and

$-\text{C(O)}-\text{NH}-\text{R}_{10}$.

- 69 -

Alternatively, in these more preferred compounds, R_5 is selected from the group consisting of:

- 5 $-S(O)_2-R_9$,
 $-S(O)_2-NH-R_{10}$,
 $-C(O)-C(O)-R_{10}$,
 $-R_9$, and
 $-C(O)-C(O)-OR_{10}$.

Most preferably, in these more preferred compounds,

10 m is 1;

T_1 is O or S;

15 R_{13} is H or a $-C_{1-4}$ straight or branched alkyl group optionally substituted with $-Ar_3$, $-OH$, $-OR_9$, or $-CO_2H$, wherein the R_9 is a $-C_{1-4}$ branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1 ;

R_{21} is $-H$ or $-CH_3$;

20 R_{51} is a C_{1-6} straight or branched alkyl group optionally substituted with Ar_3 , wherein Ar_3 is phenyl, optionally substituted by $-Q_1$;

Ar_2 is (hh);

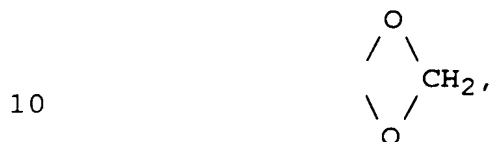
Y is O, and

25 Ar_3 is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl benzofuranyl, and indolyl;

- 70 -

Ar₄ is phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl;

each Q₁ is independently selected from the group consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅ wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is -C(O)-R₁₀, -OR₉, -NHR₉, and



wherein each R₉ and R₁₀ are independently a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃ wherein Ar₃ is phenyl;

provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃.

Other more preferred compounds of embodiment C employ formula (II) wherein R₁ is (e10), X₅ is CH, R₃ is -C(O)-H, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R₅ is selected from the group consisting of:

-C(O)-R₁₀,
-C(O)O-R₉, and
-C(O)-NH-R₁₀.

Alternatively, in these more preferred compounds, R₅ is selected from the group consisting of:

-S(O)₂-R₉,
-S(O)₂-NH-R₁₀,

- 71 -

-C(O)-C(O)-R₁₀,
-R₉, and
-C(O)-C(O)-OR₁₀.

Most preferably, in these more preferred compounds,

5 m is 1;

T₁ is O or S;

10 R₁₃ is H or a -C₁₋₄ straight or branched alkyl
group optionally substituted with -Ar₃, -OH, -OR₉, or
-CO₂H, wherein the R₉ is a -C₁₋₄ branched or straight
alkyl group, wherein Ar₃ is morpholinyl or phenyl,
wherein the phenyl is optionally substituted with Q₁;

R₂₁ is -H or -CH₃;

15 R₅₁ is a C₁₋₆ straight or branched alkyl group
optionally substituted with Ar₃, wherein Ar₃ is phenyl,
optionally substituted by -Q₁;

Ar₂ is (hh);

Y is O, and

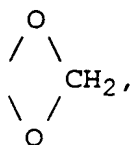
20 Ar₃ is phenyl, naphthyl, thienyl, quinolinyl,
isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl,
benzotriazolyl, benzimidazolyl, thienothienyl,
imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl
benzofuranyl, and indolyl;

25 Ar₄ is phenyl, tetrazolyl, pyridinyl, oxazolyl,
naphthyl, pyrimidinyl, or thienyl;

- 72 -

each Q_1 is independently selected from the group consisting of $-NH_2$, $-Cl$, $-F$, $-Br$, $-OH$, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

5



10 wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

15 provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$,

20 Other more preferred compounds of embodiment C employ formula (II) wherein R_1 is (e10) and X_5 is CH , R_3 is $-CO-CH_2-T_1-R_{11}$, and R_{11} is $-Ar_4$, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R_5 is selected from the group consisting of:

25 $-C(O)-R_{10}$,
 $-C(O)O-R_9$, and
 $-C(O)-NH-R_{10}$.

Alternatively, in these more preferred compounds, R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,

- 73 -

-S(O)₂-NH-R₁₀,
-C(O)-C(O)-R₁₀,
-R₉, and
-C(O)-C(O)-OR₁₀.

5 Most preferably, in these more preferred compounds,

m is 1;

T₁ is O or S;

10 R₁₃ is H or a -C₁₋₄ straight or branched alkyl group optionally substituted with -Ar₃, -OH, -OR₉, or -CO₂H, wherein the R₉ is a -C₁₋₄ branched or straight alkyl group, wherein Ar₃ is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q₁;

R₂₁ is -H or -CH₃;

15 R₅₁ is a C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein Ar₃ is phenyl, optionally substituted by -Q₁;

Ar₂ is (hh);

Y is O, and

20

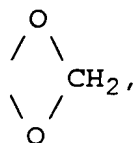
Ar₃ is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl
25 benzofuranyl, and indolyl;

Ar₄ is phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl;

- 74 -

each Q_1 is independently selected from the group consisting of $-NH_2$, $-Cl$, $-F$, $-Br$, $-OH$, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

5



10 wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

15 provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

20 Other preferred compounds of embodiment C employ formula (II) wherein R_1 is (e10), X_5 is N, and the other substituents are as defined above.

More preferred compounds of embodiment C, employ formula (II) wherein R_1 is (e10), X_5 is N, R_3 is $CO-Ar_2$, and the other substituents are as defined above.

25 Other more preferred compounds of embodiment C, employ formula (II) wherein R_1 is (e10), X_5 is N, R_3 is $-C(O)-CH_2-T_1-R_{11}$, R_{11} is $-(CH_2)_{1-3}-Ar_4$, and the other substituents are as defined above.

30 Other more preferred compounds of embodiment C, employ formula (II) wherein R_1 is (e10) and X_5 is N and:

- 75 -

R_3 is $-C(O)-CH_2-T_1-R_{11}$;

T_1 is O; and

R_{11} is $-C(O)-Ar_4$, and the other substituents are as defined above.

5 More preferably, in these more preferred compounds, R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$, and

$-C(O)-NH-R_{10}$.

10 Alternatively, in these more preferred compounds, R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,

$-S(O)_2-NH-R_{10}$,

$-C(O)-C(O)-R_{10}$,

15 $-R_9$, and

$-C(O)-C(O)-OR_{10}$.

Most preferably, in these more preferred compounds, R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,

20 $-S(O)_2-NH-R_{10}$,

$-C(O)-C(O)-R_{10}$,

$-R_9$, and

$-C(O)-C(O)-OR_{10}$.

m is 1;

25

T_1 is O or S;

R_{13} is H or a $-C_{1-4}$ straight or branched alkyl group optionally substituted with $-Ar_3$, $-OH$, $-OR_9$, or $-CO_2H$, wherein the R_9 is a $-C_{1-4}$ branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1 ;

30

- 76 -

R_{21} is -H or -CH₃;

R_{51} is a C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein Ar₃ is phenyl, optionally substituted by -Q₁;

5 Ar₂ is (hh);

Y is O, and

10 Ar₃ is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl;

Ar₄ is phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl;

15 each Q₁ is independently selected from the group consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅ wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is -C(O)-R₁₀, -OR₉, -NHR₉, and



25 wherein each R₉ and R₁₀ are independently a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃ wherein Ar₃ is phenyl;

30 provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃.

- 77 -

Other more preferred compounds of embodiment C, employ formula (II) wherein R_1 is (e10), X_5 is N, R_3 is $-C(O)-H$, and the other substituents are as defined above.

5 More preferably, in these more preferred compounds, R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,
 $-C(O)O-R_9$, and
 $-C(O)-NH-R_{10}$.

10 Alternatively, in these more preferred compounds, R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,
 $-S(O)_2-NH-R_{10}$,
 $-C(O)-C(O)-R_{10}$,
15 $-R_9$, and
 $-C(O)-C(O)-OR_{10}$.

Most preferably, in these more preferred compounds,

m is 1;

20 T_1 is O or S;

R_{13} is H or a $-C_{1-4}$ straight or branched alkyl group optionally substituted with $-Ar_3$, $-OH$, $-OR_9$, or $-CO_2H$, wherein the R_9 is a $-C_{1-4}$ branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl,
25 wherein the phenyl is optionally substituted with Q_1 ;

R_{21} is $-H$ or $-CH_3$;

R_{51} is a C_{1-6} straight or branched alkyl group optionally substituted with Ar_3 , wherein Ar_3 is phenyl, optionally substituted by $-Q_1$;

- 78 -

Ar₂ is (hh);

Y is O, and

Ar₃ is phenyl, naphthyl, thienyl, quinolinyl,
 5 isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl,
 benzotriazolyl, benzimidazolyl, thienothienyl,
 imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl
 benzofuranyl, and indolyl;

Ar₄ is phenyl, tetrazolyl, pyridinyl, oxazolyl,
 10 naphthyl, pyrimidinyl, or thienyl;

each Q₁ is independently selected from the group
 consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅
 wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is
 -C(O)-R₁₀, -OR₉, -NHR₉, and



20 wherein each R₉ and R₁₀ are independently a -C₁₋₆
 straight or branched alkyl group optionally substituted
 with Ar₃ wherein Ar₃ is phenyl;

provided that when -Ar₃ is substituted with a Q₁
 25 group which comprises one or more additional -Ar₃
 groups, said additional -Ar₃ groups are not substituted
 with another -Ar₃.

Other more preferred compounds of embodiment
 C, employ formula (II) wherein R₁ is (e10), X₅ is N, R₃
 30 is -CO-CH₂-T₁-R₁₁, R₁₁ is -Ar₄, and the other
 substituents are as defined above.

- 79 -

More preferably, in these more preferred compounds, R_5 is selected from the group consisting of:

- 5 $-C(O)-R_{10}$,
 $-C(O)O-R_9$, and
 $-C(O)-NH-R_{10}$.

Alternatively, in these more preferred compounds, R_5 is selected from the group consisting of:

- 10 $-S(O)_2-R_9$,
 $-S(O)_2-NH-R_{10}$,
 $-C(O)-C(O)-R_{10}$,
 $-R_9$, and
 $-C(O)-C(O)-OR_{10}$.

Most preferably, in these more preferred compounds

15 m is 1;

T_1 is O or S;

20 R_{13} is H or a $-C_{1-4}$ straight or branched alkyl group optionally substituted with $-Ar_3$, $-OH$, $-OR_9$, or $-CO_2H$, wherein the R_9 is a $-C_{1-4}$ branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1 ;

R_{21} is $-H$ or $-CH_3$;

25 R_{51} is a C_{1-6} straight or branched alkyl group optionally substituted with Ar_3 , wherein Ar_3 is phenyl, optionally substituted by $-Q_1$;

Ar_2 is (hh);

Y is O, and

- 80 -

Ar₃ is phenyl, naphthyl, thienyl, quinolinyl,
 isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl,
 benzotriazolyl, benzimidazolyl, thienothienyl,
 imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl
 5 benzofuranyl, and indolyl;

Ar₄ is phenyl, tetrazolyl, pyridinyl, oxazolyl,
 naphthyl, pyrimidinyl, or thienyl;

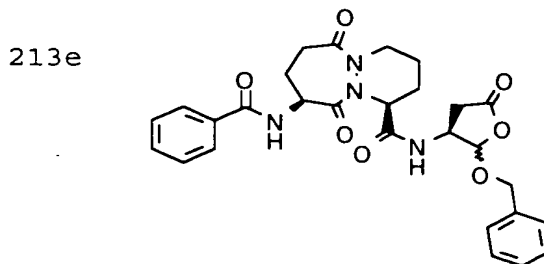
each Q₁ is independently selected from the group
 consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅
 10 wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is
 -C(O)-R₁₀, -OR₉, -NHR₉, and



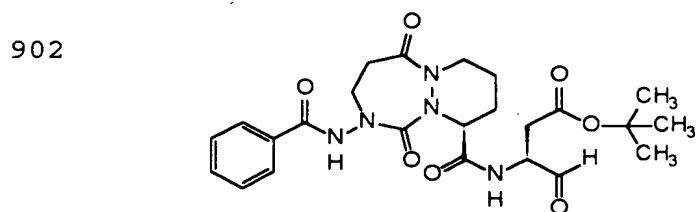
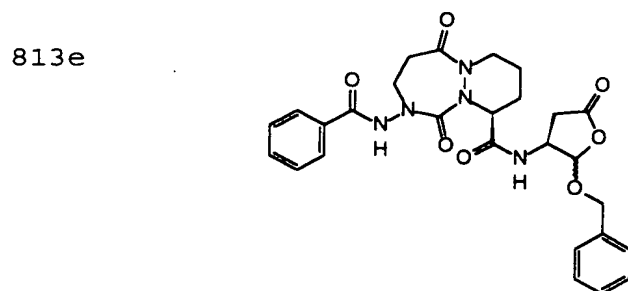
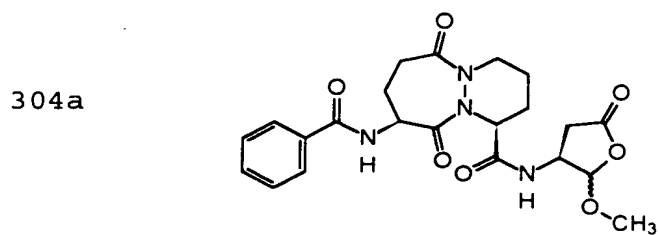
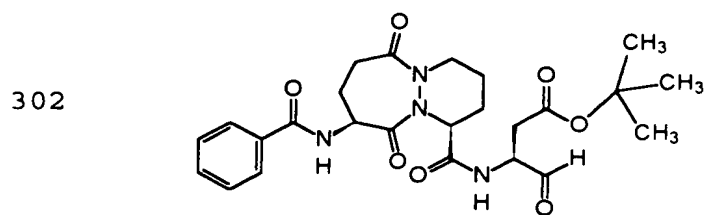
wherein each R₉ and R₁₀ are independently a -C₁₋₆
 straight or branched alkyl group optionally substituted
 with Ar₃ wherein Ar₃ is phenyl;

20 provided that when -Ar₃ is substituted with a Q₁
 group which comprises one or more additional -Ar₃
 groups, said additional -Ar₃ groups are not substituted
 with another -Ar₃.

25 Preferred compounds of embodiment B include,
 but are not limited to:

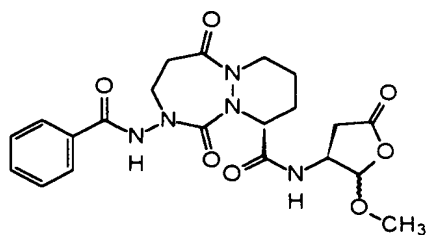


- 81 -



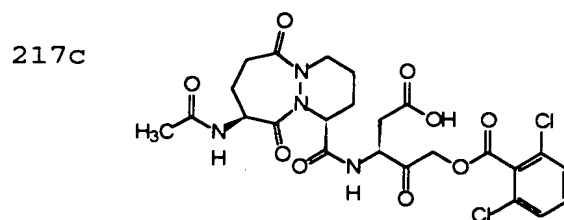
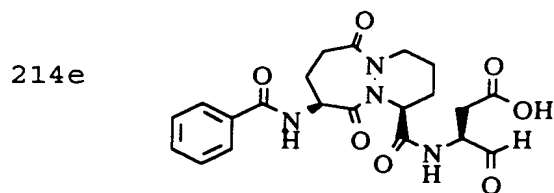
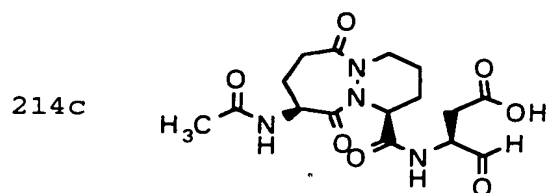
5

904a

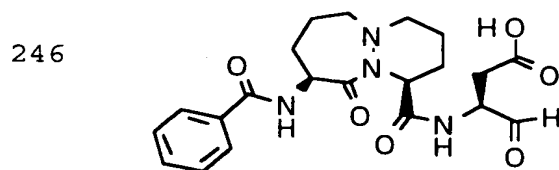
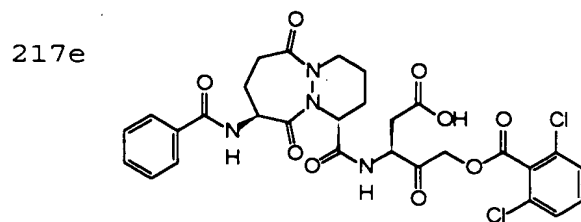
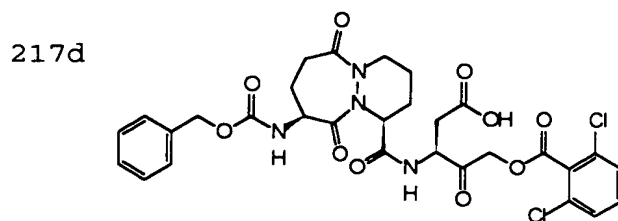


Preferred compounds of embodiment C include,
but are not limited to:

- 82 -

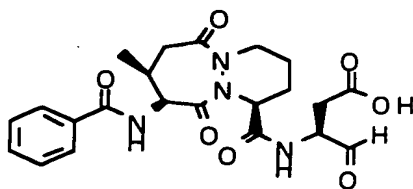


5

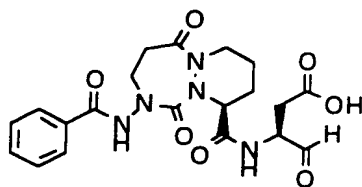


- 83 -

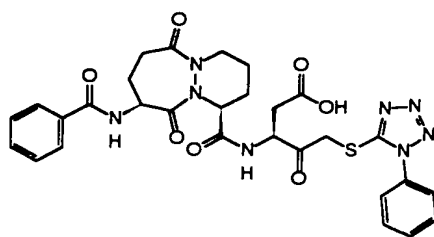
257



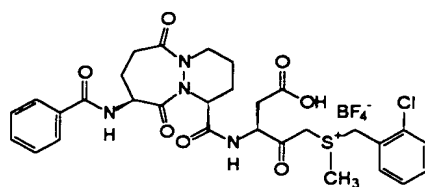
265



280

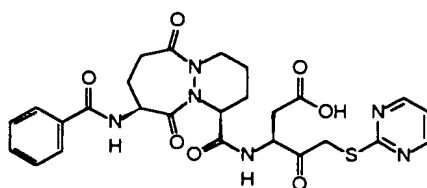


281

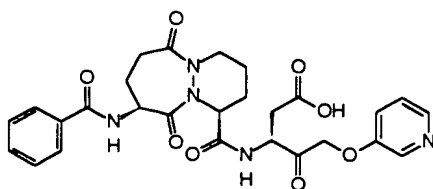


5

282

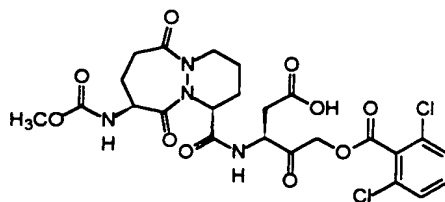


283

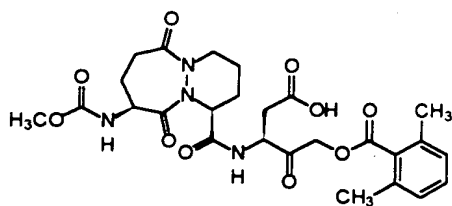


- 84 -

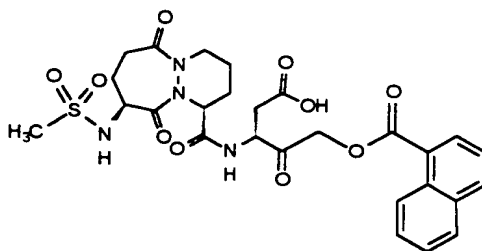
284



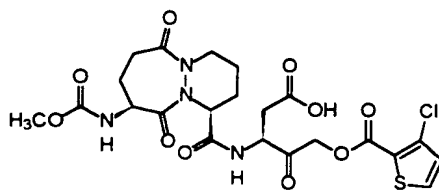
285



286

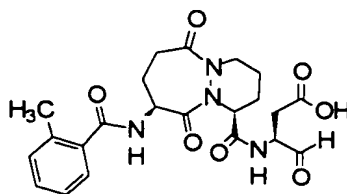


287

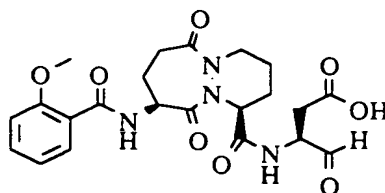


5

404

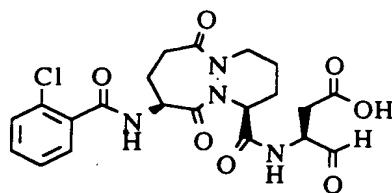


405

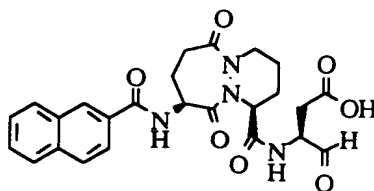


- 85 -

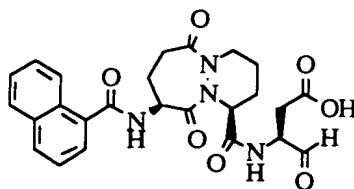
406



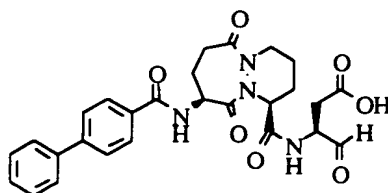
407



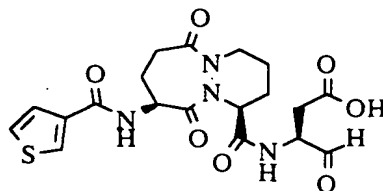
408



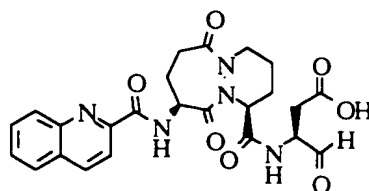
409



410

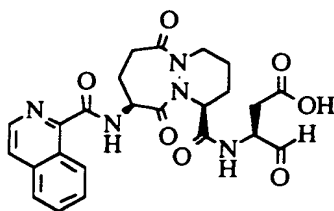


411

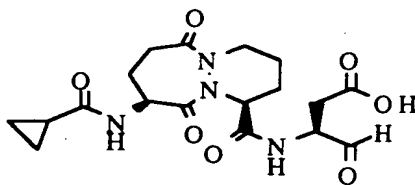


- 86 -

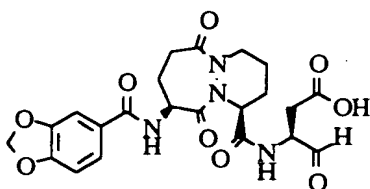
412



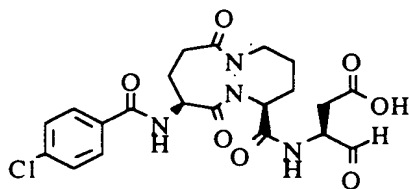
413



415

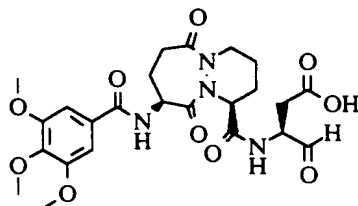


416

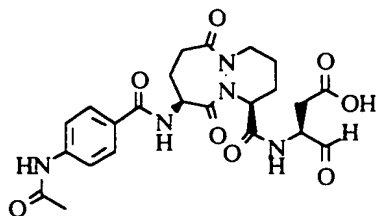


5

417

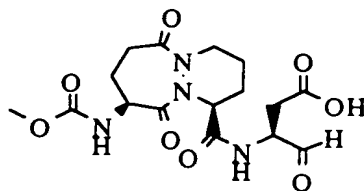


418

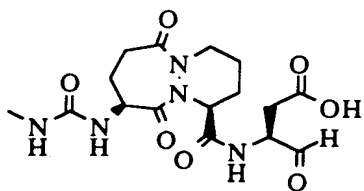


- 87 -

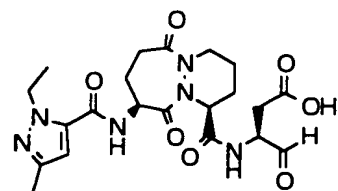
419



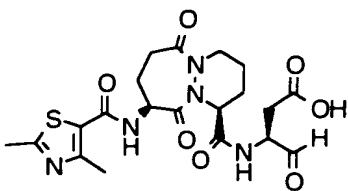
420



422

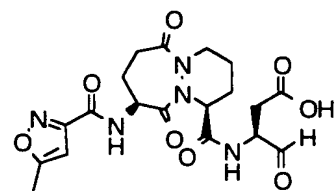


423

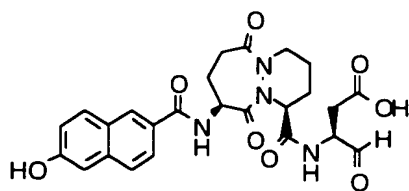


5

424

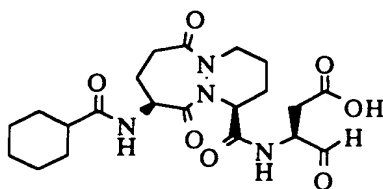


425

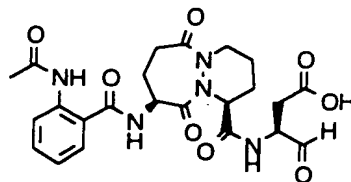


- 88 -

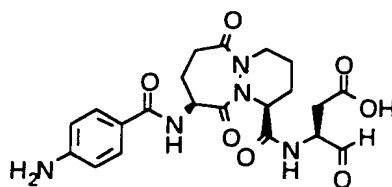
426



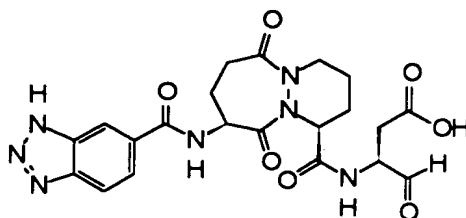
430



431

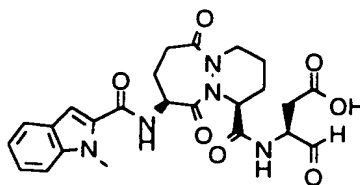


432

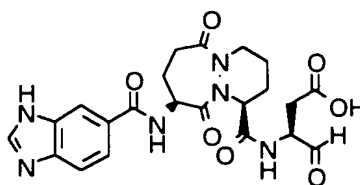


5

433

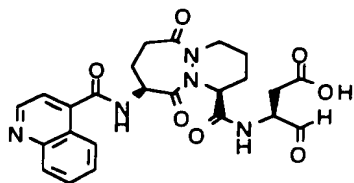


434

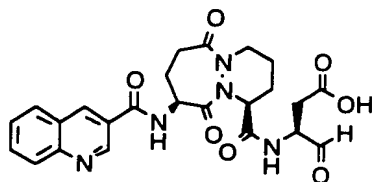


- 89 -

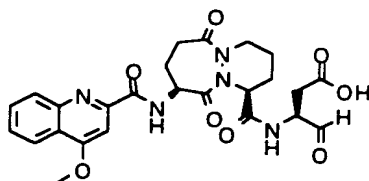
435



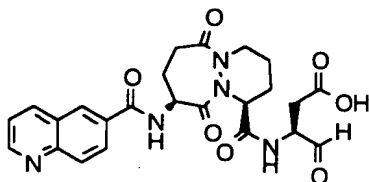
436



437

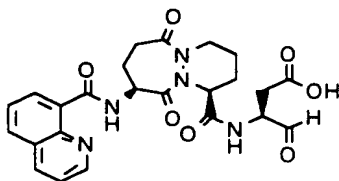


438

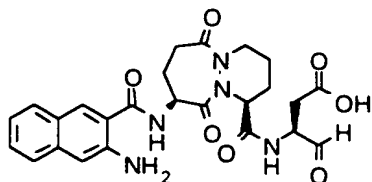


5

439

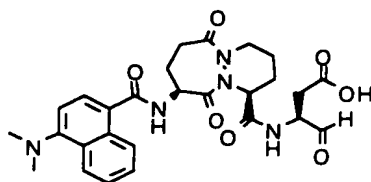


440

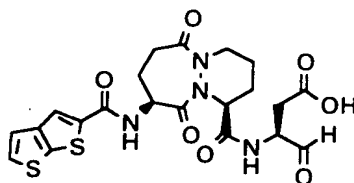


- 90 -

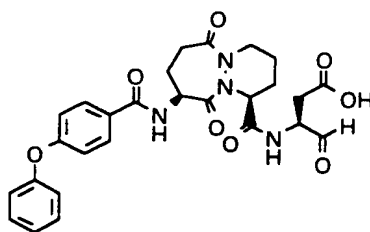
441



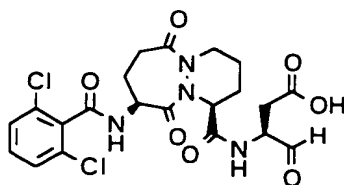
442



443

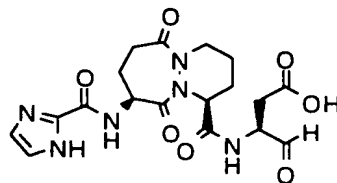


444



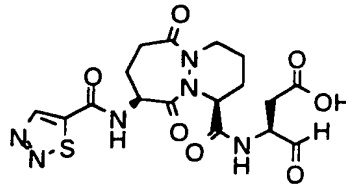
5

445

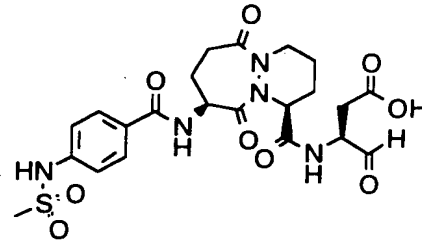


- 91 -

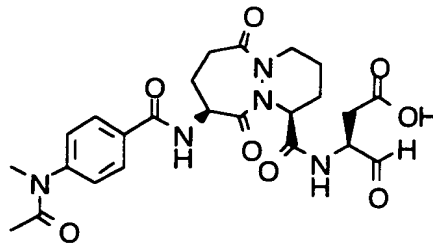
446



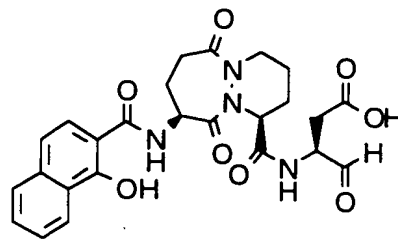
447



448

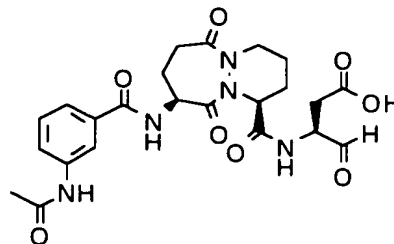


449



5

450

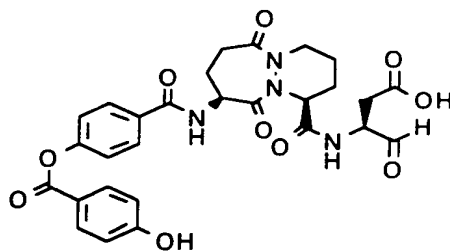


COc1ccc(cc1)C(=O)N[C@@H]2CC[C@H](C(=O)N[C@@H]3C[C@H](C(=O)O)C(=O)N3)C(=O)N2O=C(O)[C@H](N1C(=O)N[C@@H](C2=CC3=C(C=C2)S(=O)(=O)C3=CC=C2)C(=O)N1)C(=O)N[C@@H](C4=CC5=C(C=C4)S(=O)(=O)C5=CC=C4)C(=O)N1C(=O)N[C@@H](C2=CC3=C(C=C2)S(=O)(=O)C3=CC=C2)C(=O)N1O=C(O)[C@H](NC(=O)[C@@H]1N2C(=O)N(C(=O)N2C3=CC=CC=C3)C1=O)C[C@H]4C(=O)N(C(=O)O)C(=O)N4O=C(O)[C@H](NC(=O)N1CC[C@H](C(=O)N1C(=O)N2C(=O)C3=CC=C(C=C3)C(=O)O2)CC4=CC=CC=C4O)C(=O)O

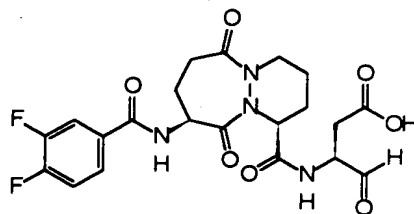
456

- 93 -

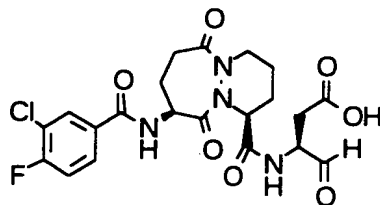
457



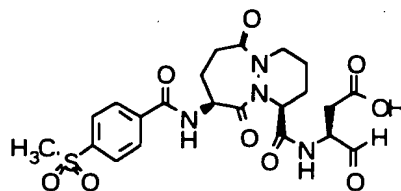
458



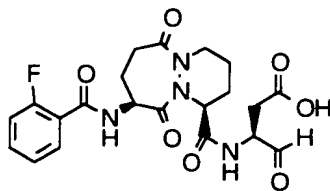
459



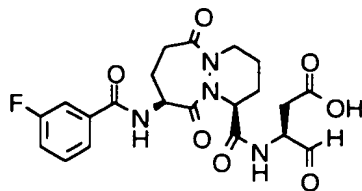
460



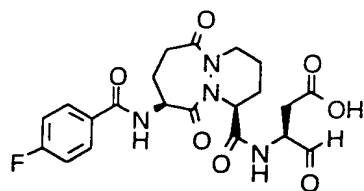
461



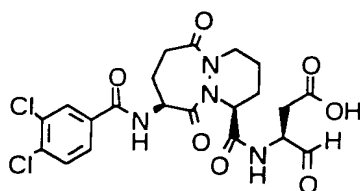
462



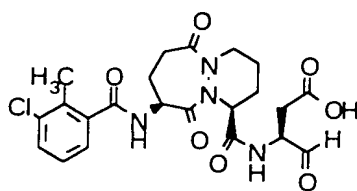
463



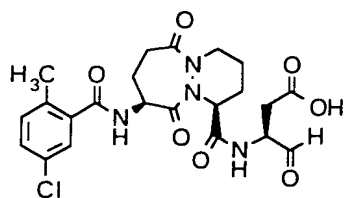
464



465

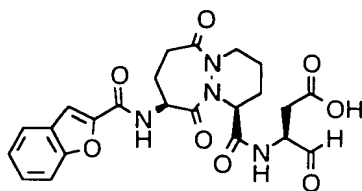


466

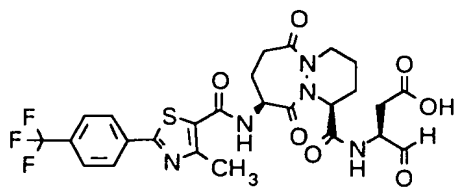


5

467

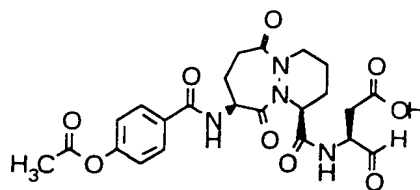


468

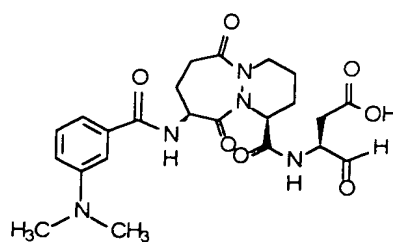


- 95 -

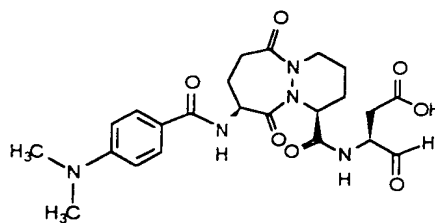
469



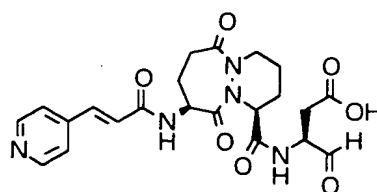
470



471

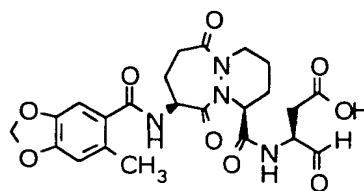


472



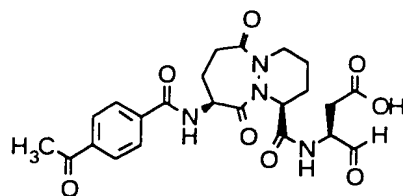
5

473

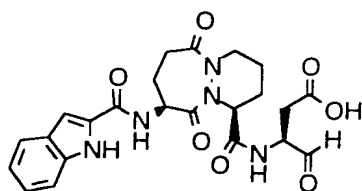


- 96 -

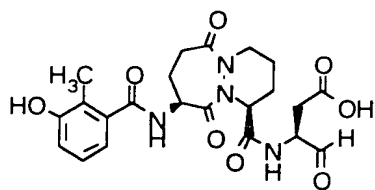
474



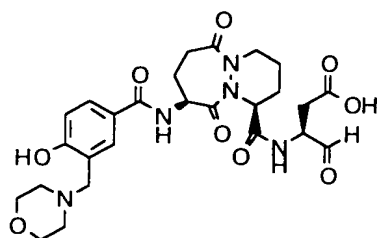
475



476

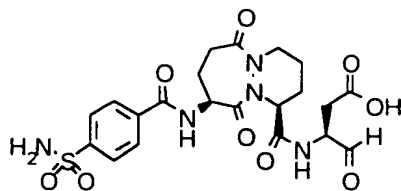


477



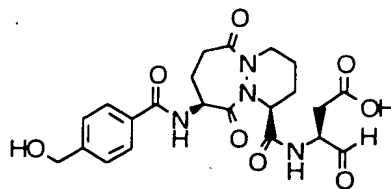
5

478

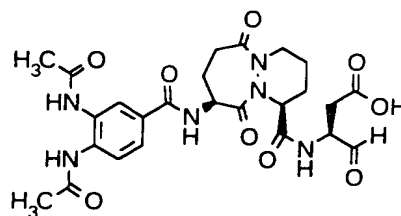


- 97 -

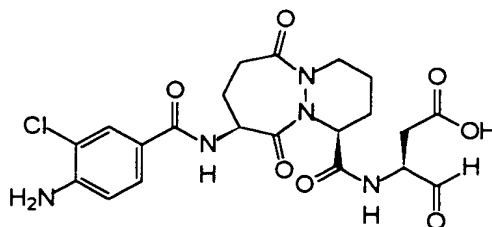
479



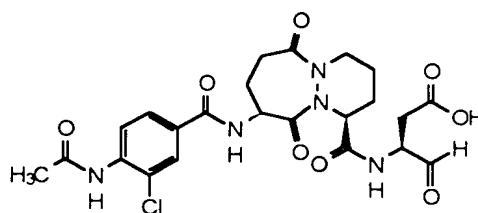
480



481

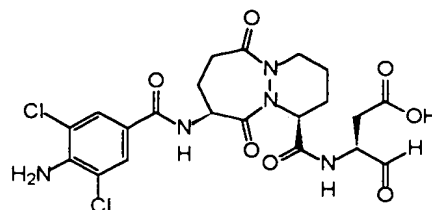


481s



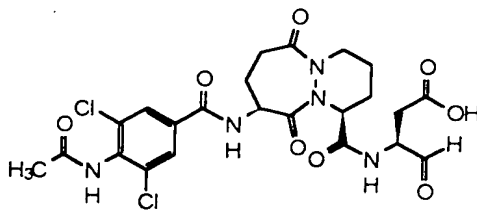
5

482

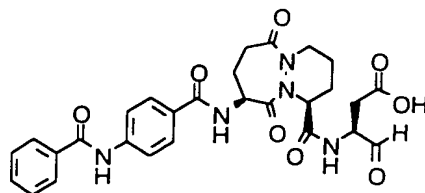


- 98 -

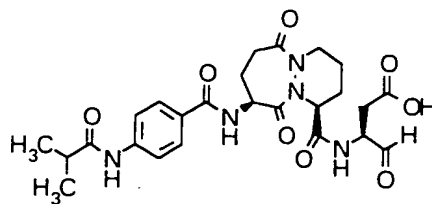
482s



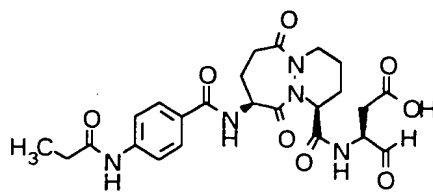
483



484

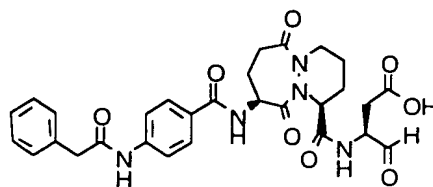


485



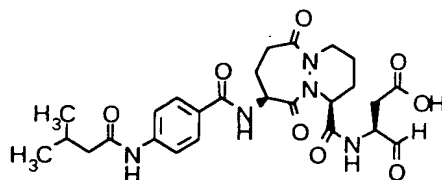
5

486

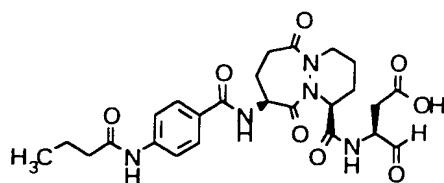


- 99 -

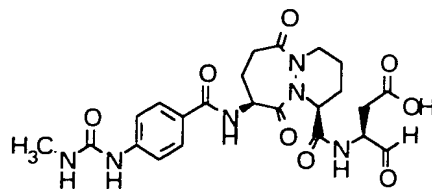
487



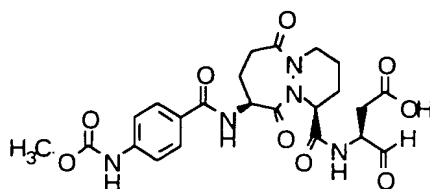
488



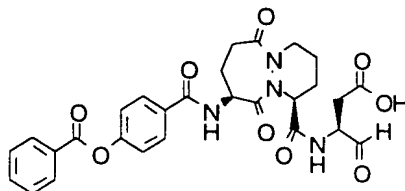
489



490

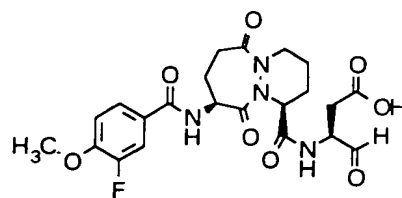


491

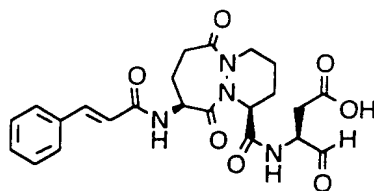


- 100 -

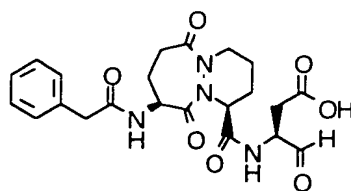
493



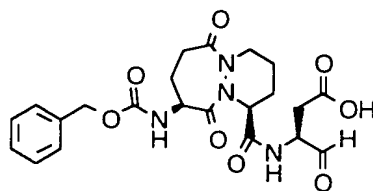
494



495

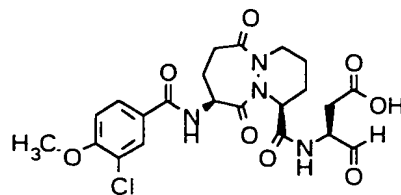


496



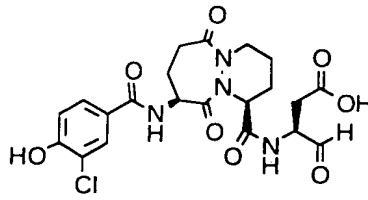
5

497

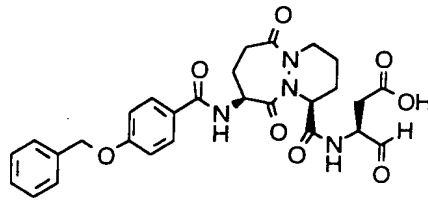


- 101 -

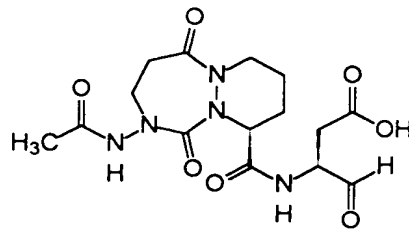
498



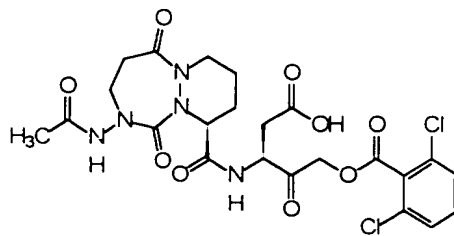
499



814c

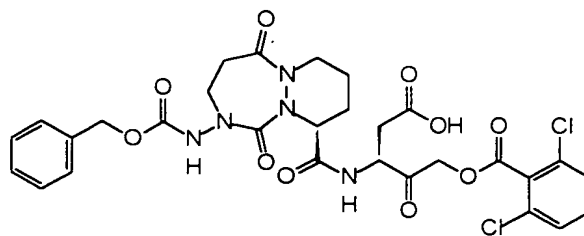


817c



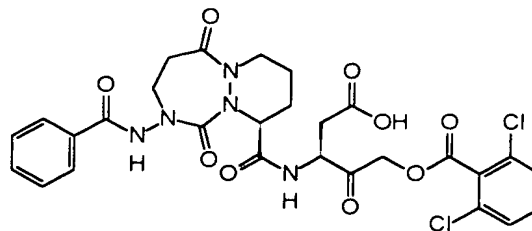
5

817d

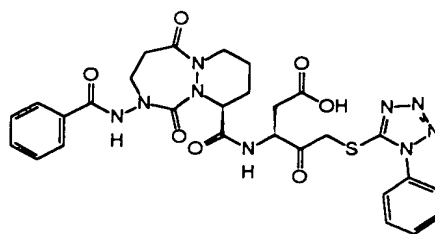


- 102 -

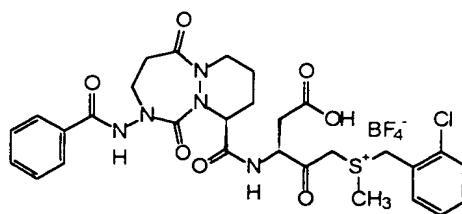
817e



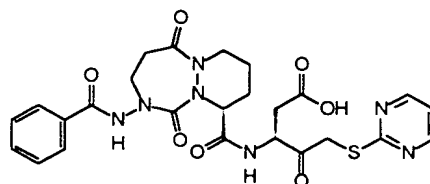
880



881

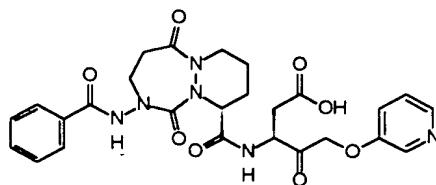


882



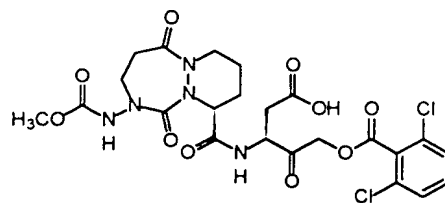
5

883

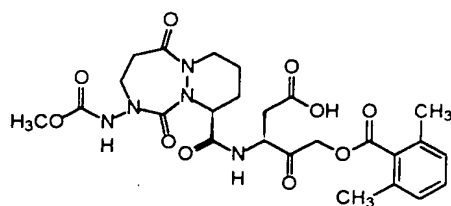


- 103 -

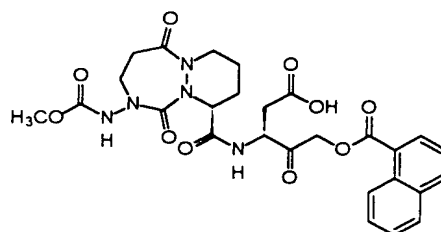
884



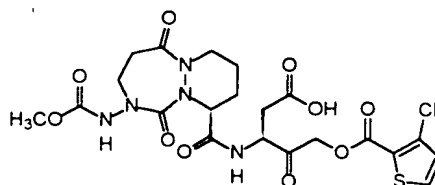
885



886

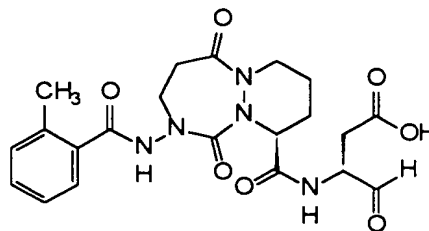


887



5

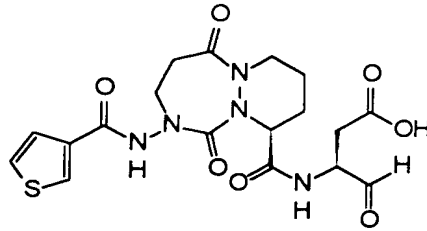
1004



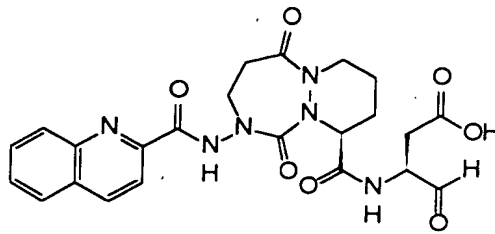
COc1ccccc1C(=O)NN2C(=O)N3CCCC4C(=O)N(C(=O)NCC(=O)O)C(=O)N3C24O=C(O)CCNC(=O)N1C(=O)N2CCCCC2C(=O)N1C(=O)N(C(=O)c3ccccc3Cl)CO=C(O)CCNC(=O)C1C(=O)N2C(=O)N(C(=O)c3ccc4ccccc4c3)CC2C1=OO=C(O)CCNC(=O)N1C(=O)N2CCCCC2C(=O)N1C(=O)N3C(=O)c4ccccc43O=C(O)C(=O)N1C(=O)N2C(=O)N(C(=O)N1Cc1ccc(cc1)-c3ccccc3)CC2

- 105 -

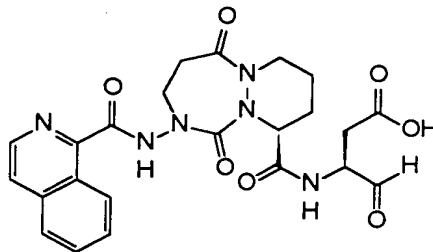
1010



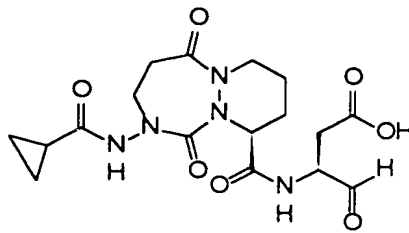
1011



1012

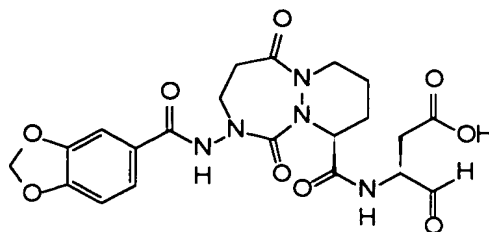


1013



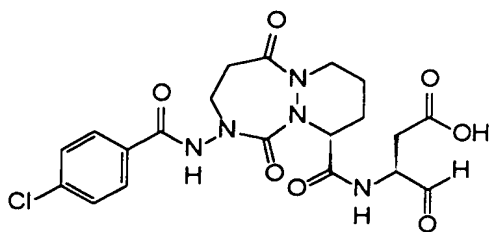
5

1015

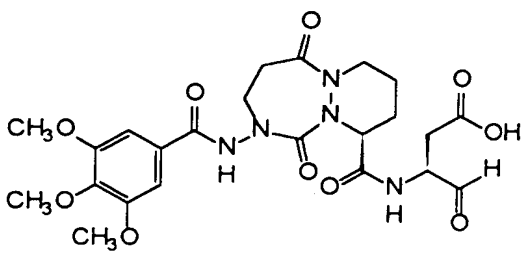


- 106 -

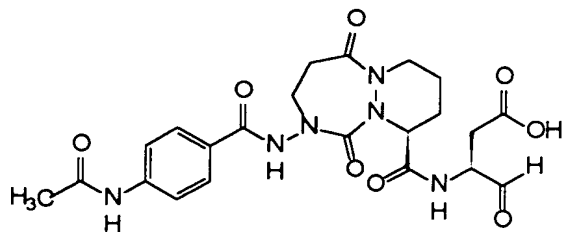
1016



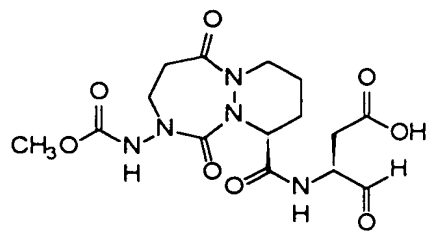
1017



1018

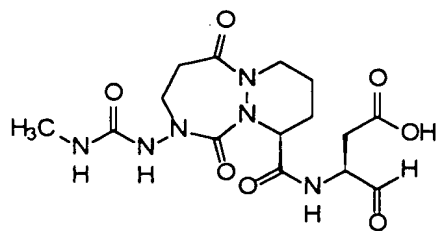


1019



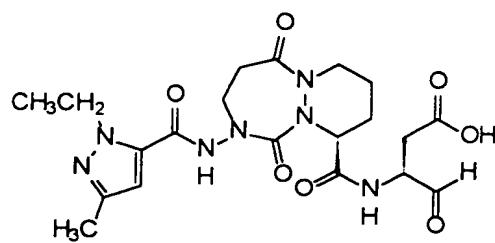
5

1020

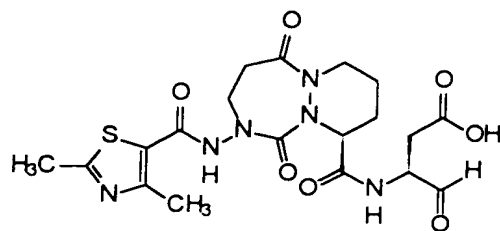


- 107 -

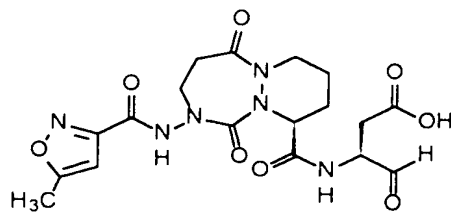
1022



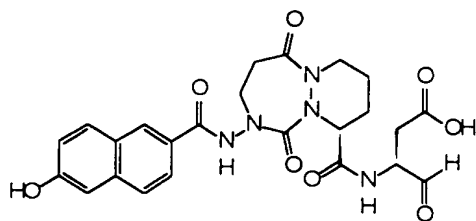
1023



1024

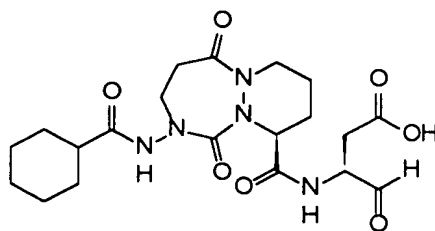


1025



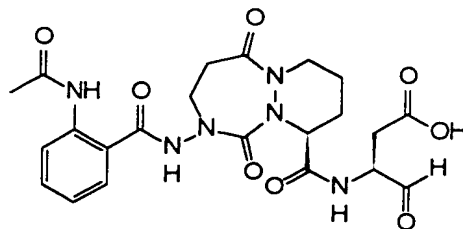
5

1026

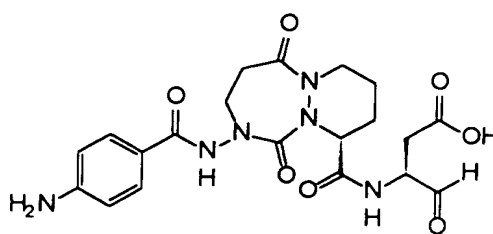


- 108 -

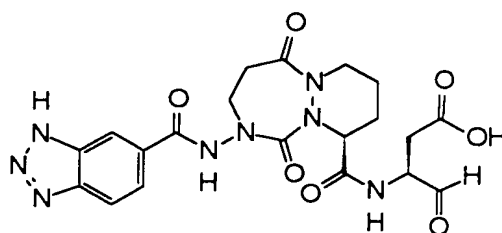
1030



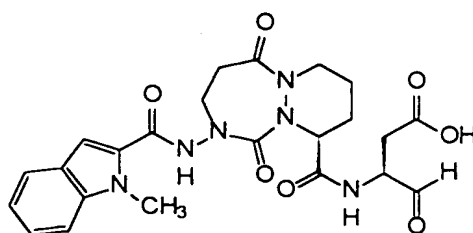
1031



1032

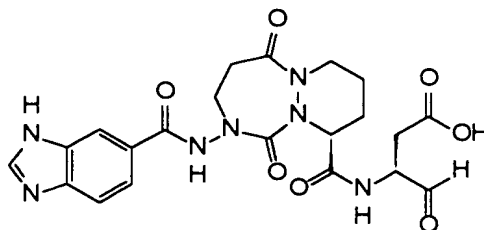


1033



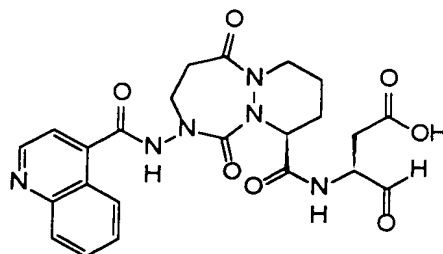
5

1034

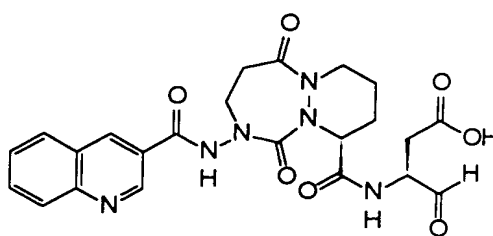


- 109 -

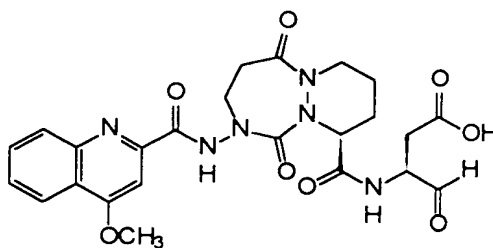
1035



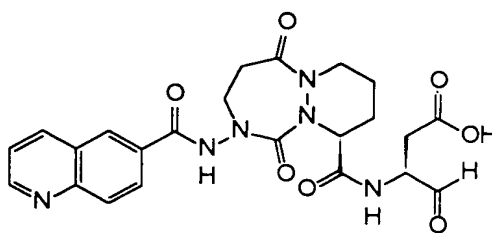
1036



1037

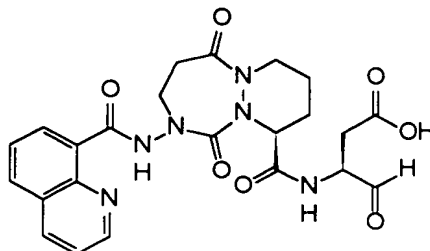


1038



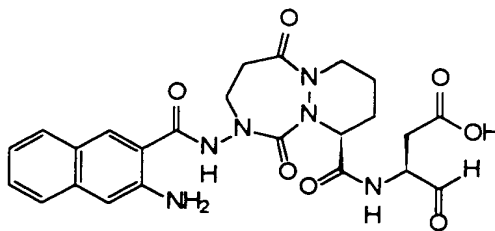
5

1039

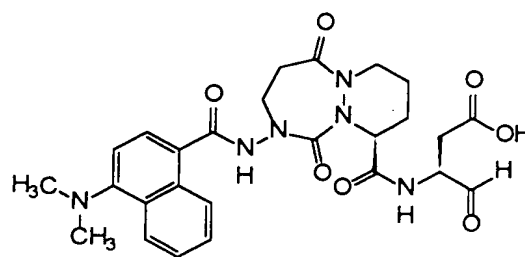


- 110 -

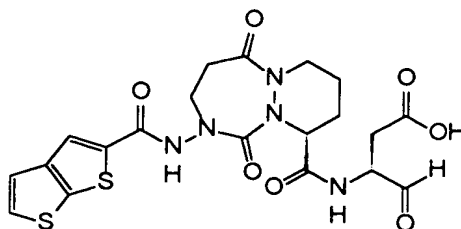
1040



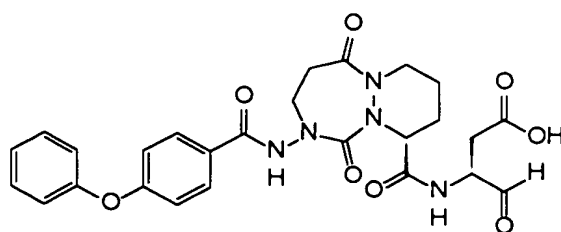
1041



1042

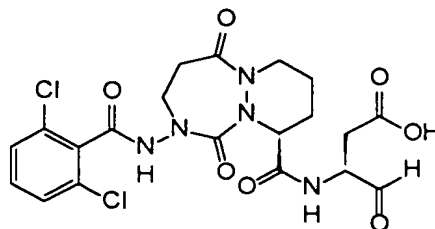


1043



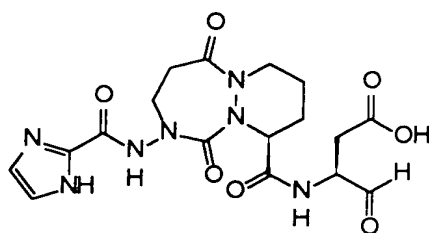
5

1044

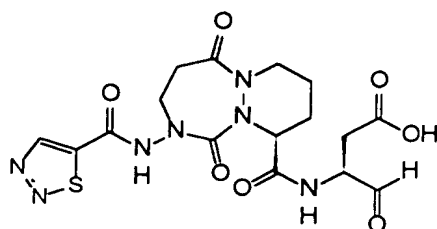


- 111 -

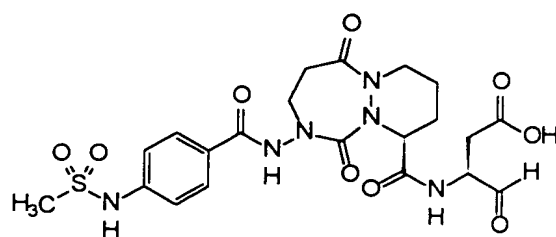
1045



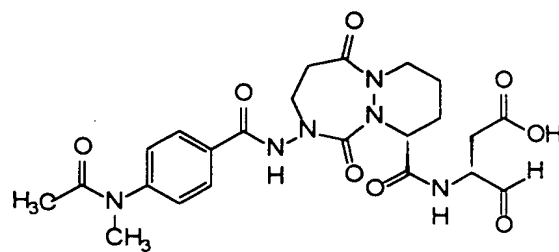
1046



1047

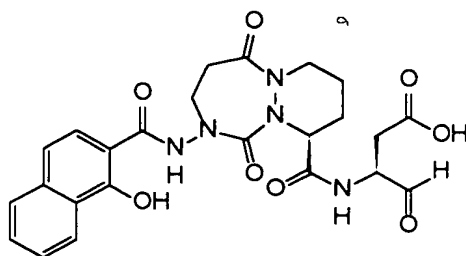


1048



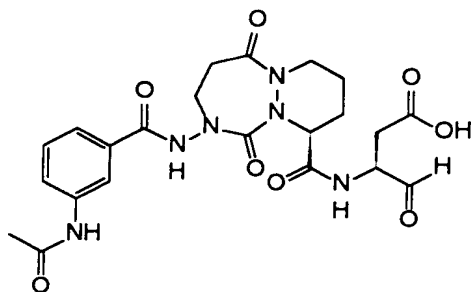
5

1049

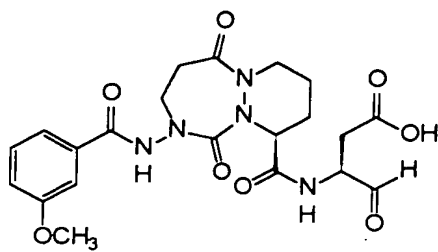


- 112 -

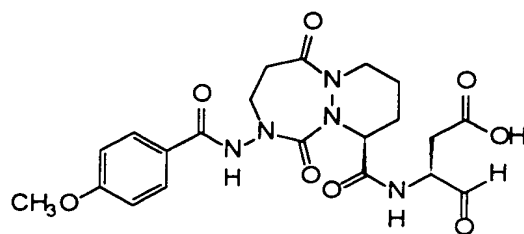
1050



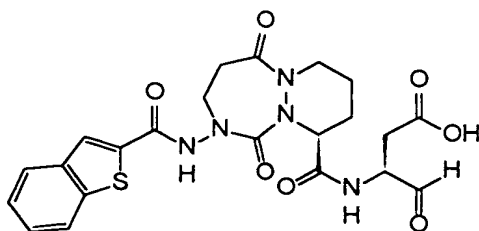
1051



1052

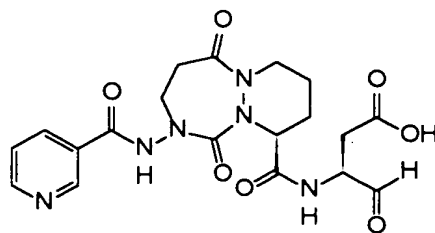


1053



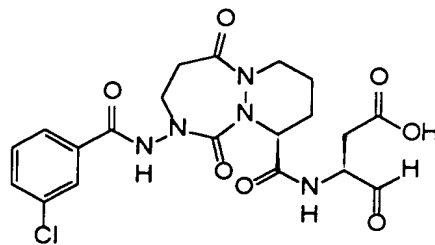
5

1054

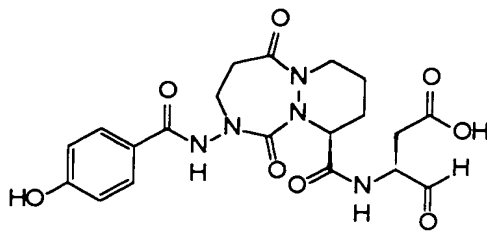


- 113 -

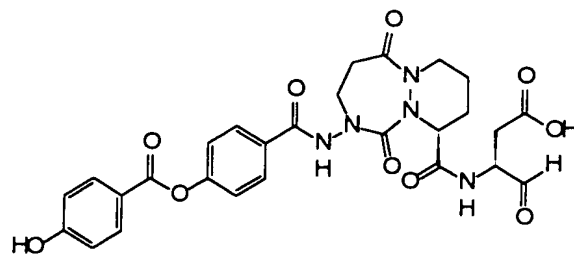
1055



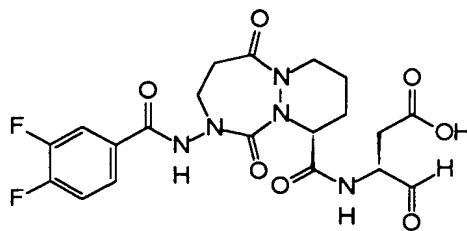
1056



1057

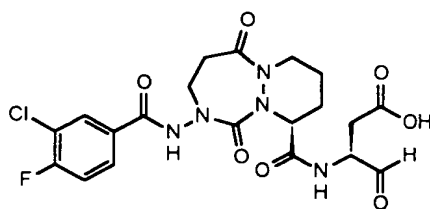


1058



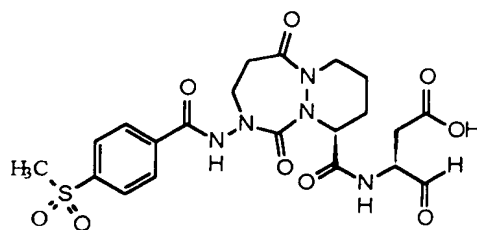
5

1059

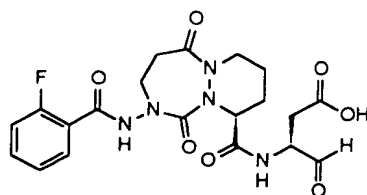


- 114 -

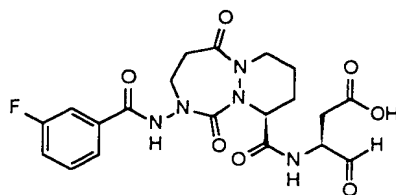
1060



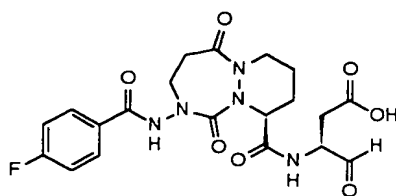
1061



1062

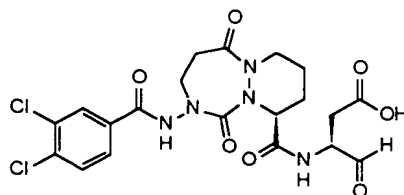


1063



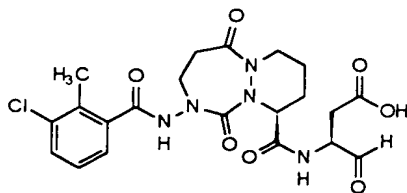
5

1064

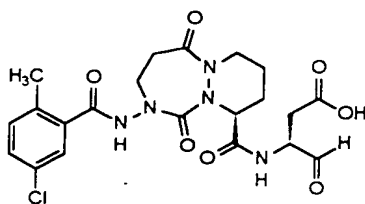


- 115 -

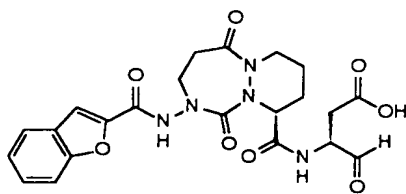
1065



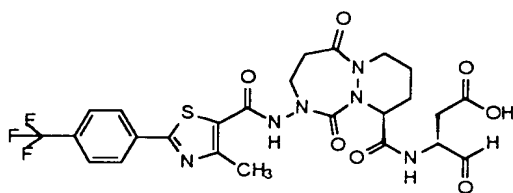
1066



1067

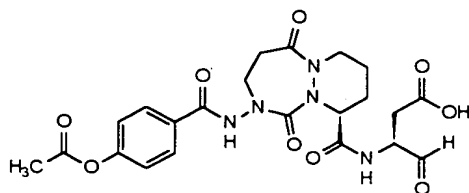


1068



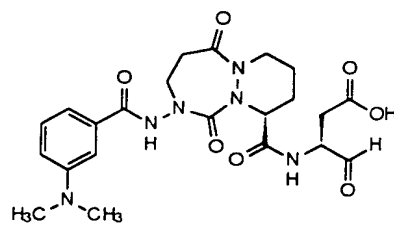
5

1069

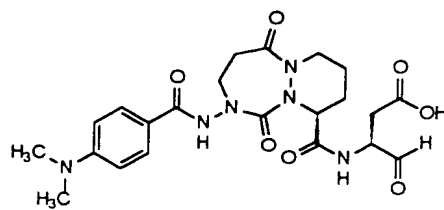


- 116 -

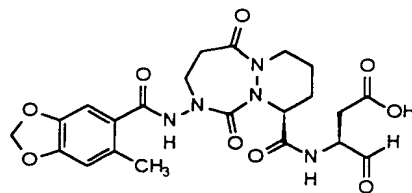
1070



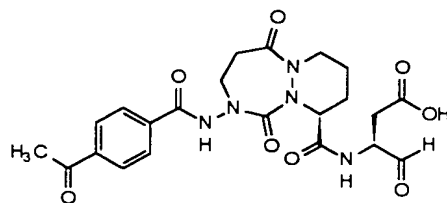
1071



1073

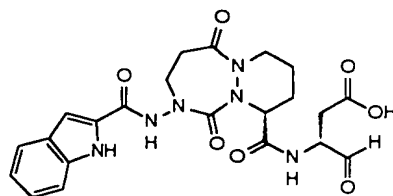


1074



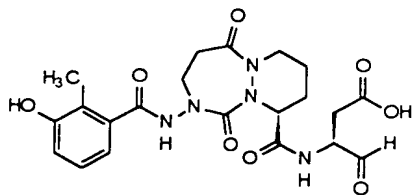
5

1075

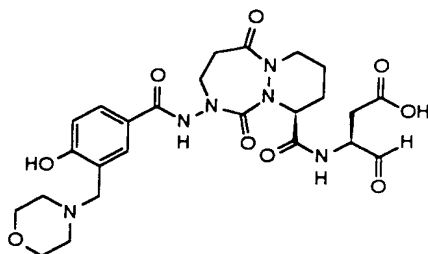


- 117 -

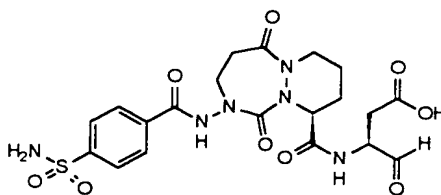
1076



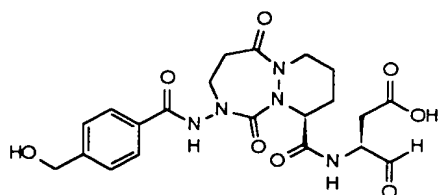
1077



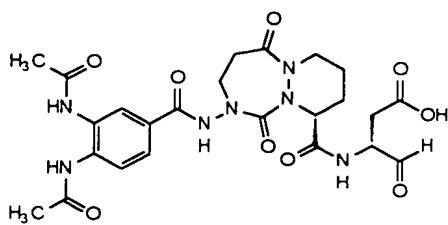
1078



1079

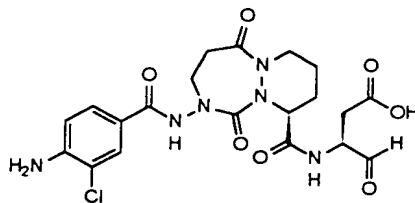


1080

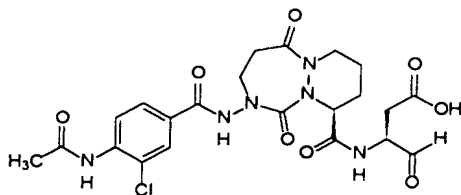


- 118 -

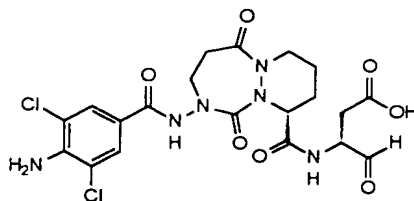
1081



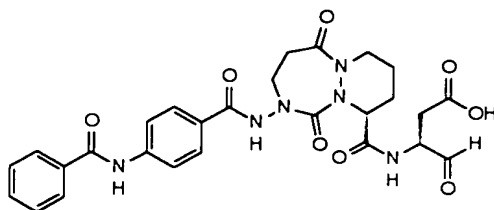
1081s



1082

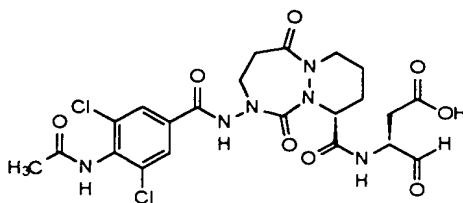


1083



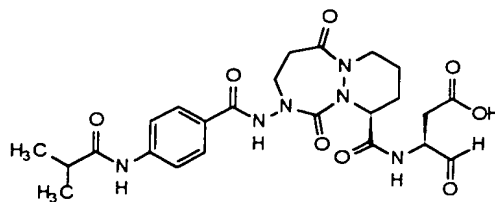
5

1082s

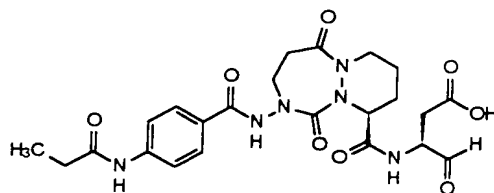


- 119 -

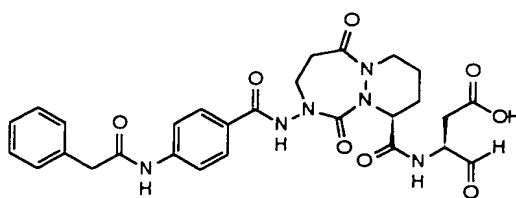
1084



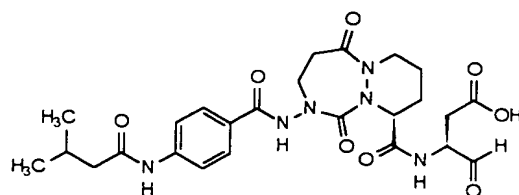
1085



1086

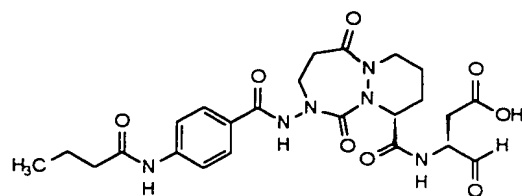


1087



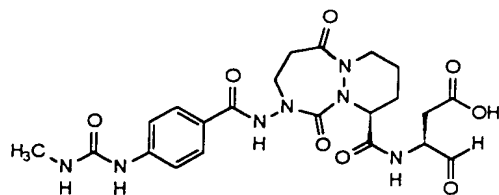
5

1088

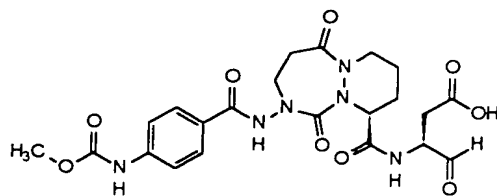


- 120 -

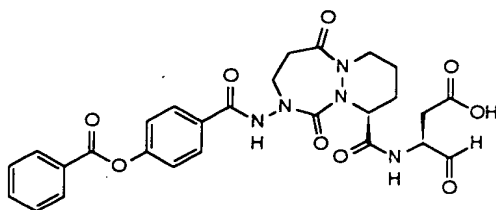
1089



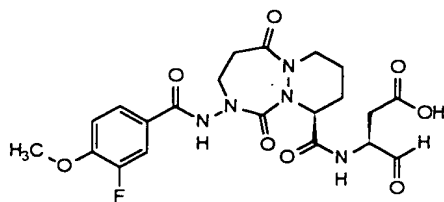
1090



1091

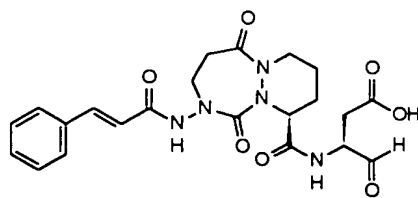


1093

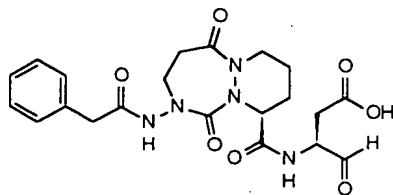


5

1094

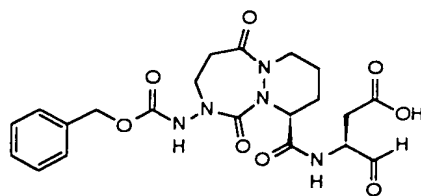


1095

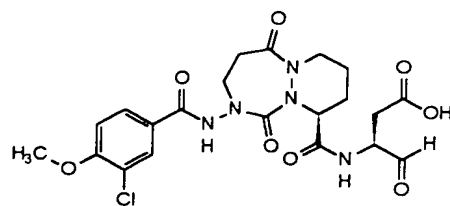


- 121 -

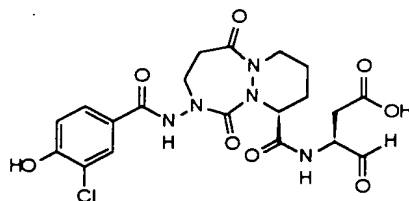
1096



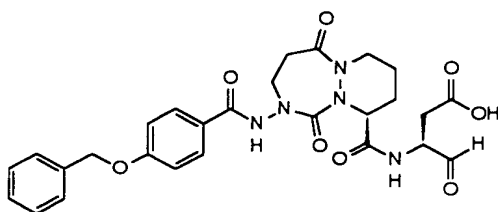
1097



1098

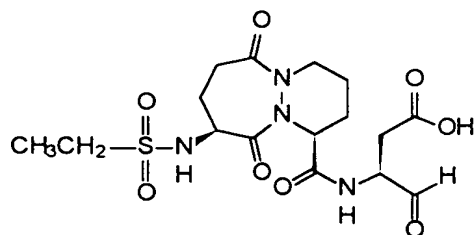


1099



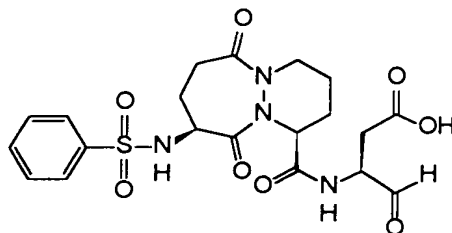
5

421

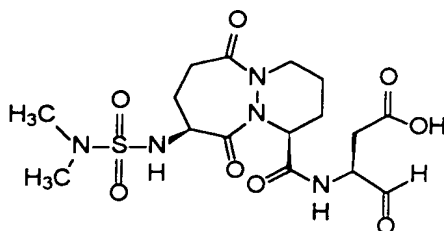


- 122 -

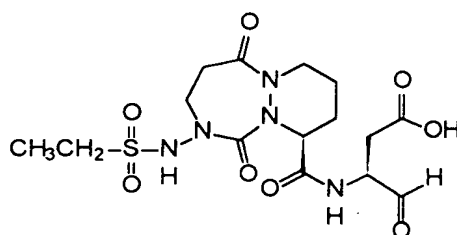
427



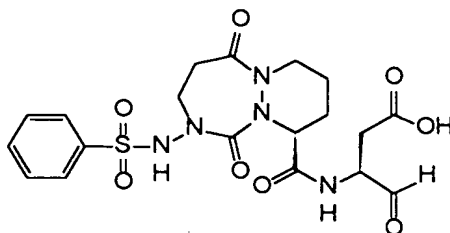
428



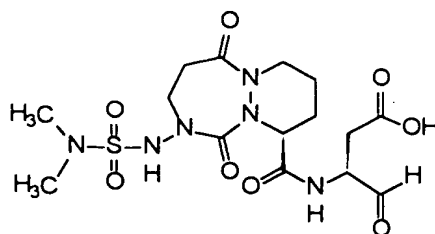
1021



1027



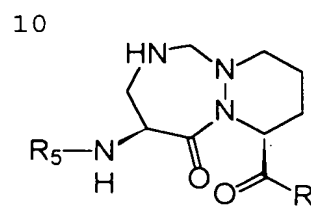
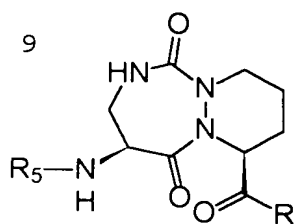
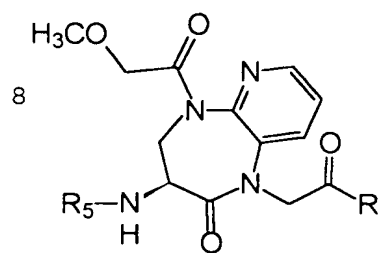
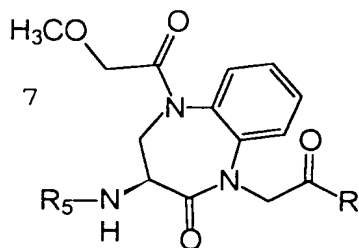
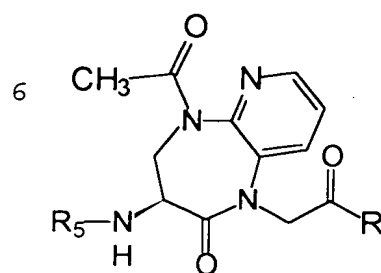
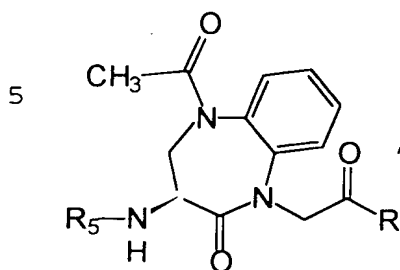
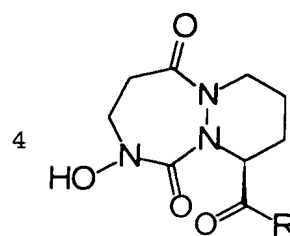
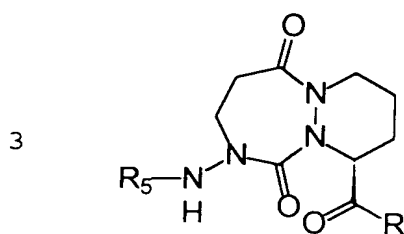
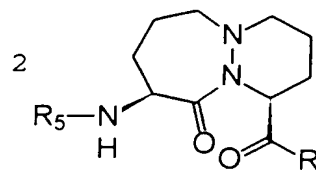
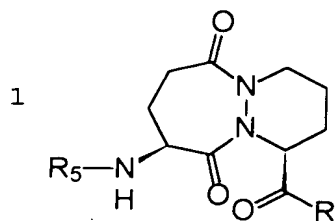
1028



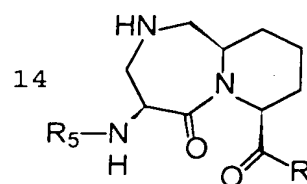
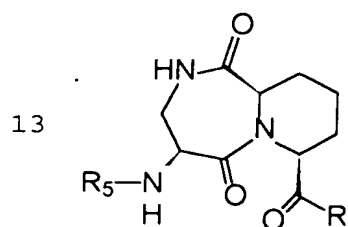
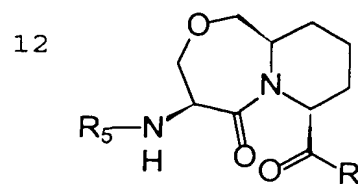
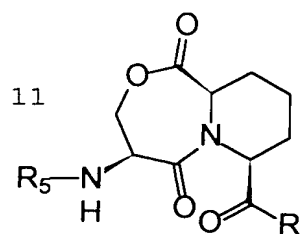
5

Specific compounds of this invention also include, but are not limited to, those compounds whose structures comprise scaffolds 1-22:

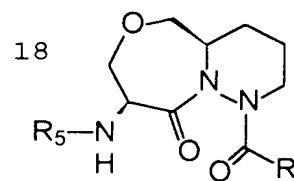
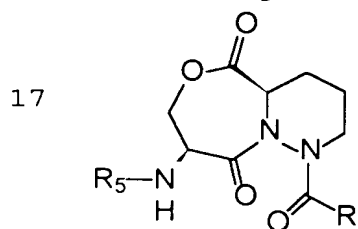
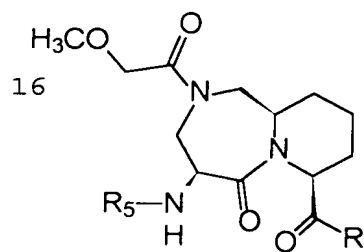
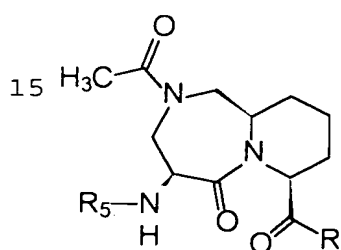
- 123 -



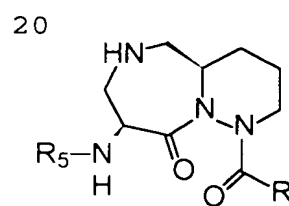
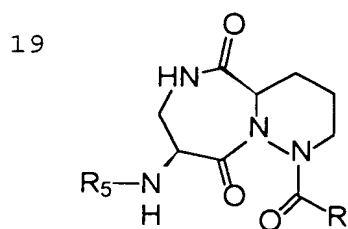
- 124 -



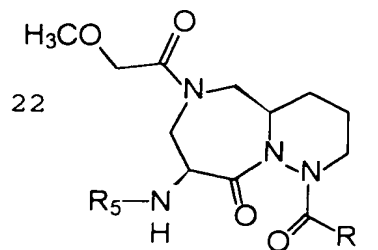
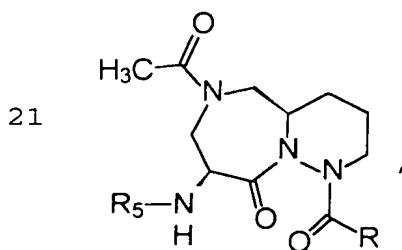
5



10

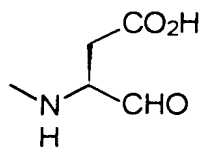


- 125 -

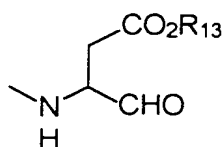


wherein:

R is



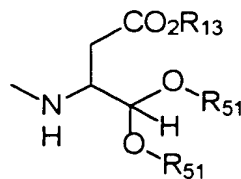
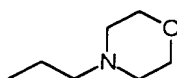
5



, wherein

R₁₃ is -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)(CH₃),
-CH₂CH₂CH₂CH₃, -CH₂-CH(CH₃)CH₃, -C(CH₃)₃, -CH₂Ph, or

10



, wherein

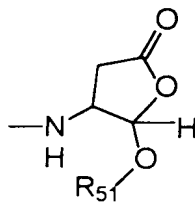
- 126 -

R_{13} is $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)(\text{CH}_3)$,
 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2-\text{CH}(\text{CH}_3)\text{CH}_3$, $-\text{C}(\text{CH}_3)_3$, $-\text{CH}_2\text{Ph}$,

or , and

5 each R_{51} is $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$,
 $-\text{CH}(\text{CH}_3)(\text{CH}_3)$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2-\text{CH}(\text{CH}_3)\text{CH}_3$, $-\text{C}(\text{CH}_3)_3$,
 $-\text{CH}_2\text{Ph}$, or taken together form a ethylenedioxy acetal
 or a propylenedioxy acetal; or

10



, wherein

R_{51} is $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)(\text{CH}_3)$,
 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2-\text{CH}(\text{CH}_3)\text{CH}_3$, $-\text{C}(\text{CH}_3)_3$, $-\text{CH}_2\text{Ph}$,
 $-\text{C}(\text{O})-\text{CH}_3$ or $-\text{C}(\text{O})-\text{Ph}$;

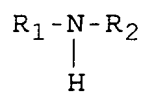
15 R_5 in each of the above compounds is the same as
 any one of the R_5 moieties shown for any one of
 compounds 139, 214c, 214e, 404-413, 415-491, 493-501.

Specific compounds of this invention also include,
 but are not limited to, compounds comprising scaffolds
 20 1-28, wherein R , R_{51} , and R_5 are as defined above, and
 in which the $-\text{C}(\text{O})-$ of the R_5 moiety of any one of
 compounds 214c, 214e, 404-413, 415-418, 422-426, 430-
 456, 458-466, 468, 470-471, 473-491, 493, 495, 497-501
 is replaced with $-\text{CH}_2-$, $-\text{C}(\text{O})\text{C}(\text{O})-$, or $-\text{CH}_2\text{C}(\text{O})\text{C}(\text{O})-$.

25 The ICE inhibitors of another embodiment (D)
 of this invention are those of formula (I):

- 127 -

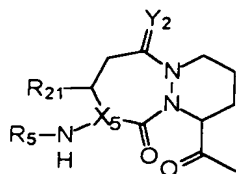
(I)



wherein:

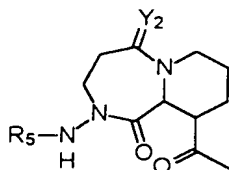
5 R_1 is selected from the group consisting of the following formulae:

(e10)



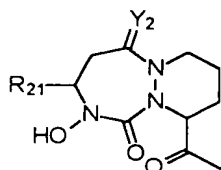
;

(e11)



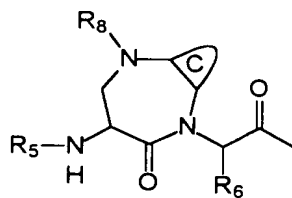
;

(e12)



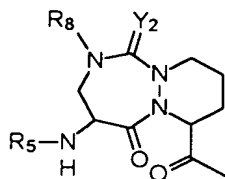
;

(w2)



;

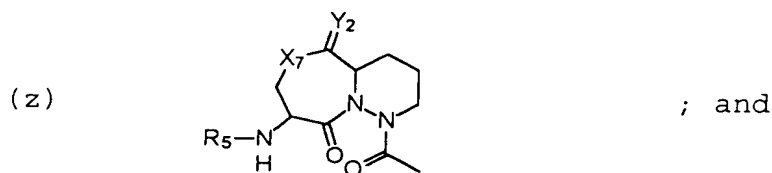
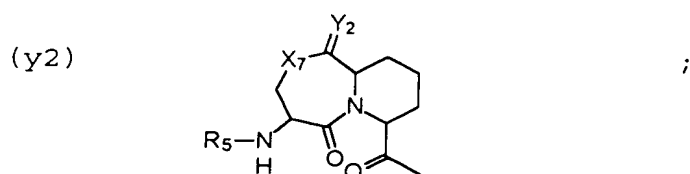
(y1)



;

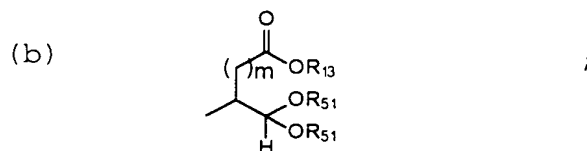
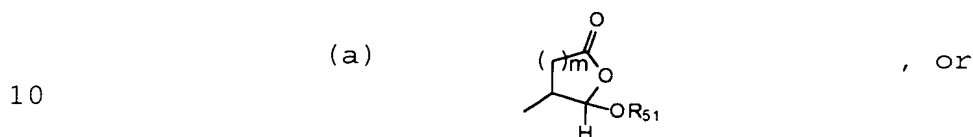
15

- 128 -



ring C is chosen from the group consisting of
 5 benzo, pyrido, thieno, pyrrolo, furano, thiazolo,
 isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo,
 cyclopentyl, and cyclohexyl;

R₂ is:



m is 1 or 2;

each R₅ is independently selected from the group
 15 consisting of:

- C(O)-R₁₀,
- C(O)O-R₉,
- C(O)-N(R₁₀)(R₁₀)
- S(O)₂-R₉,

- 129 -

5 -S(O)₂-NH-R₁₀,
 -C(O)-CH₂-O-R₉,
 -C(O)C(O)-R₁₀,
 -R₉,
 -H,
 -C(O)C(O)-OR₁₀, and
 -C(O)C(O)-N(R₉)(R₁₀);

10 X₅ is -CH- or -N-;
 | |

Y₂ is H₂ or O;

X₇ is -N(R₈)- or -O-;

15 R₆ is selected from the group consisting of -H and
 -CH₃;

 R₈ is selected from the group consisting of:
 -C(O)-R₁₀,
 -C(O)O-R₉,
 20 -C(O)-N(H)-R₁₀,
 -S(O)₂-R₉,
 -S(O)₂-NH-R₁₀,
 -C(O)-CH₂-OR₁₀,
 -C(O)C(O)-R₁₀;
 25 -C(O)-CH₂N(R₁₀)(R₁₀),
 -C(O)-CH₂C(O)-O-R₉,
 -C(O)-CH₂C(O)-R₉,
 -H, and
 -C(O)-C(O)-OR₁₀;

30 each R₉ is independently selected from the group
 consisting of -Ar₃ and a -C₁₋₆ straight or branched
 alkyl group optionally substituted with Ar₃, wherein

- 130 -

the -C₁₋₆ alkyl group is optionally unsaturated;

5 each R₁₀ is independently selected from the group consisting of -H, -Ar₃, a C₃₋₆ cycloalkyl group, and a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein the -C₁₋₆ alkyl group is optionally unsaturated;

10 R₁₃ is selected from the group consisting of H, Ar₃, and a C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, -CONH₂, -OR₅, -OH, -OR₉, or -CO₂H;

each R₅₁ is independently selected from the group consisting of R₉, -C(O)-R₉, -C(O)-N(H)-R₉, or each R₅₁ taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-;

15 each R₂₁ is independently selected from the group consisting of -H or a -C₁₋₆ straight or branched alkyl group;

20 each Ar₃ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO₂, =N-, and -NH-,
25 said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q₁;

30

each Q₁ is independently selected from the group

- 131 -

consisting of $-\text{NH}_2$, $-\text{CO}_2\text{H}$, $-\text{Cl}$, $-\text{F}$, $-\text{Br}$, $-\text{I}$, $-\text{NO}_2$, $-\text{CN}$,
 $=\text{O}$, $-\text{OH}$, -perfluoro C_{1-3} alkyl, R_5 , $-\text{OR}_5$, $-\text{NHR}_5$, OR_9 ,
 $-\text{N}(\text{R}_9)(\text{R}_{10})$, R_9 , $-\text{C}(\text{O})-\text{R}_{10}$, and



10 provided that when $-\text{Ar}_3$ is substituted with a Q_1 group which comprises one or more additional $-\text{Ar}_3$ groups, said additional $-\text{Ar}_3$ groups are not substituted with another $-\text{Ar}_3$.

15 Preferably, R_5 is selected from the group consisting of:

$-\text{C}(\text{O})-\text{R}_{10}$,
 $-\text{C}(\text{O})\text{O}-\text{R}_9$, and
 $-\text{C}(\text{O})-\text{NH}-\text{R}_{10}$.

20 Alternatively, R_5 is selected from the group consisting of:

$-\text{S}(\text{O})_2-\text{R}_9$,
 $-\text{S}(\text{O})_2-\text{NH}-\text{R}_{10}$,
 $-\text{C}(\text{O})-\text{C}(\text{O})-\text{R}_{10}$,
 $-\text{R}_9$, and
 25 $-\text{C}(\text{O})-\text{C}(\text{O})-\text{OR}_{10}$.

More preferably:

m is 1;

30 R_{13} is H or a $-\text{C}_{1-4}$ straight or branched alkyl group optionally substituted with $-\text{Ar}_3$, $-\text{OH}$, $-\text{OR}_9$, or $-\text{CO}_2\text{H}$, wherein the R_9 is a $-\text{C}_{1-4}$ branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1 ;

- 132 -

R_{21} is -H or -CH₃;

R_{51} is a C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein Ar₃ is phenyl, optionally substituted by -Q₁;

5

each Ar₃ cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by -Q₁;

each Q₁ is independently selected from the group consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅ wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is -C(O)-R₁₀, -OR₉, -N(R₉)(R₁₀), and

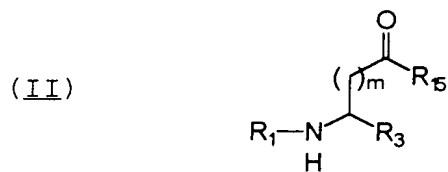


wherein each R₉ and R₁₀ are independently a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃ wherein Ar₃ is phenyl;

provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃.

The ICE inhibitors of another embodiment (E) of this invention are those of formula (II):

- 133 -

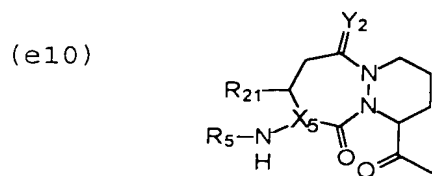


wherein:

m is 1 or 2;

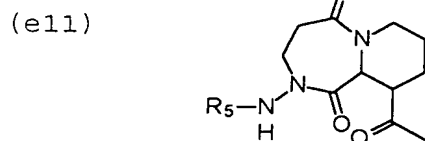
5

R_1 is selected from the group consisting of the following formulae:



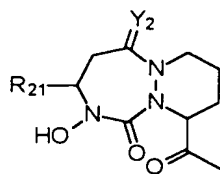
;

10



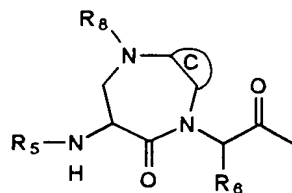
;

(e12)



;

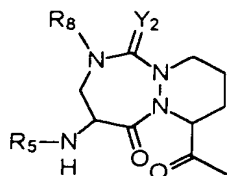
(w2)



;

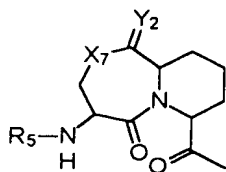
- 134 -

(y1)



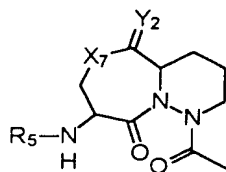
;

(y2)



;

(z)



; and

5

ring C is chosen from the group consisting of
benzo, pyrido, thieno, pyrrolo, furano, thiazolo,
isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo,
cyclopentyl, and cyclohexyl;

10

R₃ is selected from the group consisting of:

- CN,
- C(O)-H,
- C(O)-CH₂-T₁-R₁₁,
- C(O)-CH₂-F,
- C=N-O-R₉, and
- CO-Ar₂;

15

each R₅ is independently selected from the group
consisting of:

- C(O)-R₁₀,
- C(O)O-R₉,
- C(O)-N(R₁₀)(R₁₀)
- S(O)₂-R₉,
- S(O)₂-NH-R₁₀,

20

- 135 -

$-C(O)-CH_2-O-R_9$,
 $-C(O)C(O)-R_{10}$,
 $-R_9$,
 $-H$,
5 $-C(O)C(O)-OR_{10}$, and
 $-C(O)C(O)-N(R_9)(R_{10})$;

X_5 is $-CH-$ or $-N-$;
 $\quad \quad \quad | \quad \quad \quad |$

10 Y_2 is H_2 or O ;

X_7 is $-N(R_8)-$ or $-O-$;

each T_1 is independently selected from the group consisting of $-O-$, $-S-$, $-S(O)-$, and $-S(O)_2-$;

15 R_6 is selected from the group consisting of $-H$ and $-CH_3$;

R_8 is selected from the group consisting of:

20 $-C(O)-R_{10}$,
 $-C(O)O-R_9$,
 $-C(O)-NH-R_{10}$,
 $-S(O)_2-R_9$,
 $-S(O)_2-NH-R_{10}$,
 $-C(O)-CH_2-OR_{10}$,
25 $-C(O)C(O)-R_{10}$,
 $-C(O)-CH_2-N(R_{10})(R_{10})$,
 $-C(O)-CH_2C(O)-O-R_9$,
 $-C(O)-CH_2C(O)-R_9$,
 $-H$, and
30 $-C(O)-C(O)-OR_{10}$;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 , wherein

- 136 -

the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of $-H$, $-Ar_3$, a C_{3-6} cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 , wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

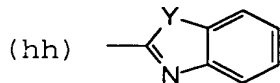
each R_{11} is independently selected from the group consisting of:

$-Ar_4$,
 $-(CH_2)_{1-3}-Ar_4$,
 $-H$, and
 $-C(O)-Ar_4$;

R_{15} is selected from the group consisting of $-OH$, $-OAr_3$, $-N(H)-OH$, and a $-OC_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, $-OH$, $-OR_9$, or $-CO_2H$;

each R_{21} is independently selected from the group consisting of $-H$ or a $-C_{1-6}$ straight or branched alkyl group;

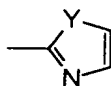
Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by $-Q_1$:



, and

- 137 -

(ii)



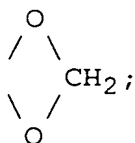
wherein each Y is independently selected from the group consisting of O and S;

5 each Ar₃ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said
10 heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO₂, =N-, and -NH-, -N(R₅)-, and -N(R₉)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings,
15 and said cyclic group optionally being singly or multiply substituted by -Q₁;

 each Ar₄ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3
20 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO₂, =N-, -NH-, -N(R₅)-, and -N(R₉)- said heterocycle group optionally
25 containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q₁;

 each Q₁ is independently selected from the group
30 consisting of -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH, -perfluoro C₁₋₃ alkyl, R₅, -OR₅, -NHR₅, OR₉, -N(R₉)(R₁₀), R₉, -C(O)-R₁₀, and

- 138 -



5

provided that when $-\text{Ar}_3$ is substituted with a Q_1 group which comprises one or more additional $-\text{Ar}_3$ groups, said additional $-\text{Ar}_3$ groups are not substituted with another $-\text{Ar}_3$.

10

Preferred compounds of embodiment E employ formula (II), wherein R_1 is (e11) and the other substituents are as defined above.

Other preferred compounds of embodiment E employ formula (II), wherein R_1 is (e12) and the other substituents are as defined above.

15

Other preferred compounds of embodiment E employ formula (II) wherein R_1 is (y1) and the other substituents are as defined above.

Other preferred compounds of embodiment E employ formula (II) wherein R_1 is (y2) and the other substituents are as defined above.

20

Other preferred compounds of embodiment E of employ formula (II) wherein R_1 is (z) and the other substituents are as defined above.

25

Other preferred compound of embodiment E employ formula (II) wherein R_1 is (w2) and the other substituents are as defined above.

More preferably, R_1 is (w2) and

- 139 -

m is 1;

ring C is benzo, pyrido, or thieno;

R₃ is selected from the group consisting of
-C(O)-H, -C(O)-Ar₂, and -C(O)CH₂-T₁-R₁₁;

5 R₅ is selected from the group consisting of:

-C(O)-R₁₀, wherein R₁₀ is -Ar₃;

-C(O)O-R₉, wherein R₉ is -CH₂-Ar₃;

-C(O)C(O)-R₁₀, wherein R₁₀ is -Ar₃;

-R₉, wherein R₉ is a C₁₋₂ alkyl group

10 substituted with -Ar₃; and

-C(O)C(O)-OR₁₀, wherein R₁₀ is -CH₂Ar₃;

T₁ is O or S;

R₆ is H;

15 R₈ is selected from the group consisting -C(O)-R₁₀,
-C(O)-CH₂-OR₁₀, and -C(O)CH₂-N(R₁₀)(R₁₀), wherein R₁₀ is
H, CH₃, or -CH₂CH₃;

R₁₁ is selected from the group consisting of -Ar₄,
-(CH₂)₁₋₃-Ar₄, and -C(O)-Ar₄;

20 R₁₅ is -OH or -OC₁₋₄ straight or branched alkyl
group optionally substituted with -Ar₃, -OH, -OR₉, or
-CO₂H, wherein the R₉ is a -C₁₋₄ branched or straight
alkyl group, wherein Ar₃ is morpholinyl or phenyl,
wherein the phenyl is optionally substituted with Q₁;

25 Ar₂ is (hh);

Y is O;

- 140 -

each Ar₃ cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by -Q₁;

each Ar₄ cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, naphthyl, pyridinyl, oxazolyl, pyrimidinyl, or indolyl, said cyclic group optionally being singly or multiply substituted by -Q₁;

each Q₁ is independently selected from the group consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅ wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is -C(O)-R₁₀, -OR₉, -N(R₉)(R₁₀), and



wherein each R₉ and R₁₀ are independently a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃ wherein Ar₃ is phenyl;

provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃.

Other preferred compounds of embodiment E employ formula (II) wherein R₁ is (e10), X₅ is CH, and the other substituents are as defined above.

- 141 -

More preferred compounds of embodiment E employ formula (II) wherein R_1 is (e10), X_5 is CH, R_3 is CO-Ar₂, and the other substituents are as defined above.

5 Other more preferred compounds of embodiment E employ formula (II) wherein R_1 is (e10), X_5 is CH, R_3 is -C(O)-CH₂-T₁-R₁₁, R_{11} is -(CH₂)₁₋₃-Ar₄, and the other substituents are as defined above.

10 Other more preferred compounds of embodiment E employ formula (II) wherein R_1 is (e10) and X_5 is CH and R_3 is -C(O)-CH₂-T₁-R₁₁, T₁ is O, R_{11} is -C(O)-Ar₄, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R_5 is selected from the group consisting of:

15 -C(O)-R₁₀,
-C(O)O-R₉, and
-C(O)-NH-R₁₀.

Alternatively, in these more preferred compounds, R_5 is selected from the group consisting of:

20 -S(O)₂-R₉,
-S(O)₂-NH-R₁₀,
-C(O)-C(O)-R₁₀,
-R₉, and
-C(O)-C(O)-OR₁₀.

25 Most preferably, in these more preferred compounds,

m is 1;

T₁ is O or S;

R₁₅ is -OH or -OC₁₋₄ straight or branched alkyl

- 142 -

group optionally substituted with $-\text{Ar}_3$, $-\text{OH}$, $-\text{OR}_9$, or $-\text{CO}_2\text{H}$, wherein the R_9 is a $-\text{C}_{1-4}$ branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1 ;

5 R_{21} is $-\text{H}$ or $-\text{CH}_3$;

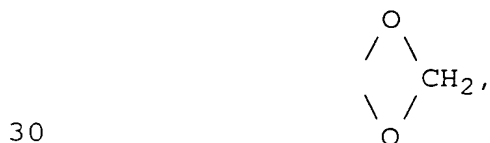
Ar_2 is (hh);

Y is O , and

10 each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl,
15 and said cyclic group optionally being singly or multiply substituted by $-\text{Q}_1$;

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl,
20 said cyclic group being singly or multiply substituted by $-\text{Q}_1$;

each Q_1 is independently selected from the group consisting of $-\text{NH}_2$, $-\text{Cl}$, $-\text{F}$, $-\text{Br}$, $-\text{OH}$, $-\text{R}_9$, $-\text{NH}-\text{R}_5$ wherein R_5 is $-\text{C}(\text{O})-\text{R}_{10}$ or $-\text{S}(\text{O})_2-\text{R}_9$, $-\text{OR}_5$ wherein R_5 is
25 $-\text{C}(\text{O})-\text{R}_{10}$, $-\text{OR}_9$, $-\text{N}(\text{R}_9)(\text{R}_{10})$, and



wherein each R_9 and R_{10} are independently a $-\text{C}_{1-6}$

- 143 -

straight or branched alkyl group optionally substituted with Ar₃ wherein Ar₃ is phenyl;

5 provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃.

10 Other more preferred compounds of embodiment E employ formula (II) wherein R₁ is (e10), X₅ is CH, R₃ is -C(O)-H, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R₅ is selected from the group consisting of:

15 -C(O)-R₁₀,
-C(O)O-R₉, and
-C(O)-NH-R₁₀.

Alternatively, in these more preferred compounds, R₅ is selected from the group consisting of:

20 -S(O)₂-R₉,
-S(O)₂-NH-R₁₀,
-C(O)-C(O)-R₁₀,
-R₉, and
-C(O)-C(O)-OR₁₀.

Most preferably, in these more preferred compounds,

25 m is 1;

R₁₅ is -OH or -OC₁₋₄ straight or branched alkyl group optionally substituted with -Ar₃, -OH, -OR₉, or -CO₂H, wherein the R₉ is a -C₁₋₄ branched or straight alkyl group, wherein Ar₃ is morpholinyl or phenyl,
30 wherein the phenyl is optionally substituted with Q₁;

- 144 -

R_{21} is -H or -CH₃;

each Ar₃ cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, said cyclic group optionally being singly or multiply substituted by -Q₁;

each Q₁ is independently selected from the group consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅ wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is -C(O)-R₁₀, -OR₉, -N(R₉)(R₁₀), and



20 wherein each R₉ and R₁₀ are independently a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃ wherein Ar₃ is phenyl;

25 provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃,

30 Other more preferred compounds of embodiment E employ formula (II) wherein R₁ is (e10) and X₅ is CH, R₃ is -CO-CH₂-T₁-R₁₁, and R₁₁ is -Ar₄, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R₅ is selected from the group consisting of:

- 145 -

-C(O)-R₁₀,
-C(O)O-R₉, and
-C(O)-NH-R₁₀.

Alternatively, in these more preferred compounds, R₅ is
5 selected from the group consisting of:

-S(O)₂-R₉,
-S(O)₂-NH-R₁₀,
-C(O)-C(O)-R₁₀,
-R₉, and
10 -C(O)-C(O)-OR₁₀.

Most preferably, in these more preferred compounds,

m is 1;

T₁ is O or S;

15 R₁₅ is -OH or a -OC₁₋₄ straight or branched alkyl
group optionally substituted with -Ar₃, -OH, -OR₉, or
-CO₂H, wherein the R₉ is a -C₁₋₄ branched or straight
alkyl group, wherein Ar₃ is morpholinyl or phenyl,
wherein the phenyl is optionally substituted with Q₁;

20 R₂₁ is -H or -CH₃;

each Ar₃ cyclic group is phenyl, naphthyl,
thienyl, quinolinyl, isoquinolinyl, pyrazolyl,
thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl,
25 thienothienyl, imidazolyl, thiadiazolyl,
benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl,
and said cyclic group optionally being singly or
multiply substituted by -Q₁;

each Ar₄ cyclic group is independently selected

- 146 -

from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl, said cyclic group optionally being singly or multiply substituted by $-Q_1$;

- 5 each Q_1 is independently selected from the group consisting of $-NH_2$, $-Cl$, $-F$, $-Br$, $-OH$, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-N(R_9)(R_{10})$, and



- 15 wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

- 20 provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

Other preferred compounds of embodiment E employ formula (II) wherein R_1 is (e10), X_5 is N, and the other substituents are as defined above.

- 25 More preferred compounds of embodiment E, employ formula (II) wherein R_1 is (e10), X_5 is N, R_3 is $CO-Ar_2$, and the other substituents are as defined above.

- 30 Other more preferred compounds of embodiment E, employ formula (II) wherein R_1 is (e10), X_5 is N, R_3 is $-C(O)-CH_2-T_1-R_{11}$, R_{11} is $-(CH_2)_{1-3}-Ar_4$, and the other substituents are as defined above.

- 147 -

Other more preferred compounds of embodiment E, employ formula (II) wherein R_1 is (e10) and X_5 is N and:

5 R_3 is $-C(O)-CH_2-T_1-R_{11}$;
 T_1 is O; and
 R_{11} is $-C(O)-Ar_4$, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R_5
10 is selected from the group consisting of:

$-C(O)-R_{10}$,
 $-C(O)O-R_9$, and
 $-C(O)-NH-R_{10}$.

Alternatively, in these more preferred compounds, R_5 is
15 selected from the group consisting of:

$-S(O)_2-R_9$,
 $-S(O)_2-NH-R_{10}$,
 $-C(O)-C(O)-R_{10}$,
 $-R_9$, and
20 $-C(O)-C(O)-OR_{10}$.

Most preferably, in these more preferred compounds,
 m is 1;

T_1 is O or S;

25 R_{15} is $-OH$ or a $-OC_{1-4}$ straight or branched alkyl group optionally substituted with $-Ar_3$, $-OH$, $-OR_9$, or $-CO_2H$, wherein the R_9 is a $-C_{1-4}$ branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1 ;

30 R_{21} is $-H$ or $-CH_3$;

- 148 -

Ar₂ is (hh);

Y is O, and

each Ar₃ cyclic group is independently selected
 5 from the set consisting of phenyl, naphthyl, thienyl,
 quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl,
 isoxazolyl, benzotriazolyl, benzimidazolyl,
 thienothienyl, imidazolyl, thiadiazolyl,
 benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl,
 10 and said cyclic group optionally being singly or
 multiply substituted by -Q₁;

each Ar₄ cyclic group is independently selected
 from the set consisting of phenyl, tetrazolyl,
 pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl,
 15 optionally being singly or multiply substituted by -Q₁;

each Q₁ is independently selected from the group
 consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅
 wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is
 -C(O)-R₁₀, -OR₉, -N(R₉)(R₁₀), and



25 wherein each R₉ and R₁₀ are independently a -C₁₋₆
 straight or branched alkyl group optionally substituted
 with Ar₃ wherein Ar₃ is phenyl;

provided that when -Ar₃ is substituted with a Q₁
 30 group which comprises one or more additional -Ar₃
 groups, said additional -Ar₃ groups are not substituted
 with another -Ar₃.

- 149 -

Other more preferred compounds of embodiment E, employ formula (II) wherein R_1 is (e10), X_5 is N, R_3 is $-C(O)-H$, and the other substituents are as defined above.

5 More preferably, in these more preferred compounds, R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,
 $-C(O)O-R_9$, and
 $-C(O)-NH-R_{10}$.

10 Alternatively, in these more preferred compounds, R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,
 $-S(O)_2-NH-R_{10}$,
 $-C(O)-C(O)-R_{10}$,
15 $-R_9$, and
 $-C(O)-C(O)-OR_{10}$.

Most preferably, in these more preferred compounds,

m is 1;

20 R_{15} is $-OH$ or $-OC_{1-4}$ straight or branched alkyl group optionally substituted with $-Ar_3$, $-OH$, $-OR_9$, or $-CO_2H$, wherein the R_9 is a $-C_{1-4}$ branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1 ;

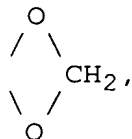
R_{21} is $-H$ or $-CH_3$;

25

- 150 -

each Ar₃ cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by -Q₁;

each Q₁ is independently selected from the group consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅ wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is -C(O)-R₁₀, -OR₉, -N(R₉)(R₁₀), and



wherein each R₉ and R₁₀ are independently a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃ wherein Ar₃ is phenyl;

provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃.

Other more preferred compounds of embodiment E, employ formula (II) wherein R₁ is (e10), X₅ is N, R₃ is -CO-CH₂-T₁-R₁₁, R₁₁ is -Ar₄, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R₅ is selected from the group consisting of:

-C(O)-R₁₀,
-C(O)O-R₉, and

- 151 -

-C(O)-NH-R₁₀.

Alternatively, in these more preferred compounds, R₅ is selected from the group consisting of:

- 5 -S(O)₂-R₉,
 -S(O)₂-NH-R₁₀,
 -C(O)-C(O)-R₁₀,
 -R₉, and
 -C(O)-C(O)-OR₁₀.

Most preferably, in these more preferred compounds

10 m is 1;

 T₁ is O or S;

 R₁₅ is -OH or -OC₁₋₄ straight or branched alkyl
15 group optionally substituted with -Ar₃, -OH, -OR₉, or
 -CO₂H, wherein the R₉ is a -C₁₋₄ branched or straight
 alkyl group, wherein Ar₃ is morpholinyl or phenyl,
 wherein the phenyl is optionally substituted with Q₁;

 R₂₁ is -H or -CH₃;

20 each Ar₃ cyclic group is independently selected
 from the set consisting of phenyl, naphthyl, thienyl,
 quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl,
 isoxazolyl, benzotriazolyl, benzimidazolyl,
 thienothienyl, imidazolyl, thiadiazolyl,
25 benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl,
 and said cyclic group optionally being singly or
 multiply substituted by -Q₁;

 each Ar₄ cyclic group is independently selected
 from the set consisting of phenyl, tetrazolyl,
30 pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl,

- 152 -

said cyclic group being singly or multiply substituted by $-Q_1$;

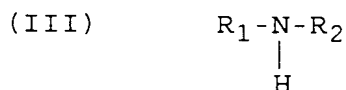
each Q_1 is independently selected from the group consisting of $-NH_2$, $-Cl$, $-F$, $-Br$, $-OH$, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-N(R_9)(R_{10})$, and



wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

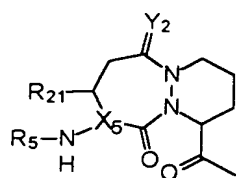
The ICE inhibitors of another embodiment (F) of this invention are those of formula (III):



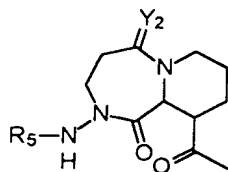
wherein:

R_1 is selected from the group consisting of the following formulae:

(e10)

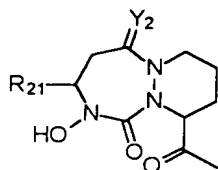


(e11)

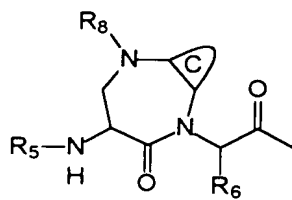


5

(e12)

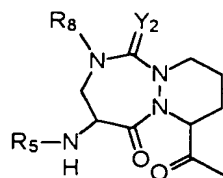


(w2)

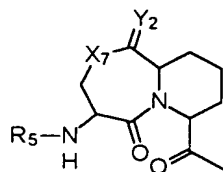


10

(y1)

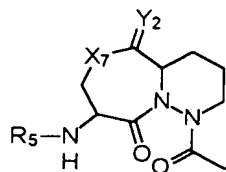


(y2)



- 154 -

(z)

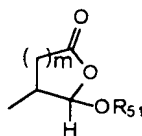


; and

ring C is chosen from the group consisting of
benzo, pyrido, thieno, pyrrolo, furano, thiazolo,
5 isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo,
cyclopentyl, and cyclohexyl;

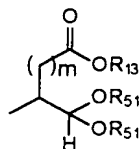
R₂ is:

(a)



, or

(b)



;

m is 1 or 2;

each R₅ is independently selected from
the group consisting of:

- C(O)-R₁₀,
- C(O)O-R₉,
- C(O)-N(R₁₀)(R₁₀)
- S(O)₂-R₉,
- S(O)₂-NH-R₁₀,
- C(O)-CH₂-O-R₉,
- C(O)C(O)-R₁₀,
- R₉,
- H,

- 155 -

-C(O)C(O)-OR₁₀, and
-C(O)C(O)-N(R₉)(R₁₀);

X₅ is CH or N;

5

Y₂ is H₂ or O;

X₇ is -N(R₈)- or -O-;

10 R₆ is selected from the group consisting of -H and
-CH₃;

R₈ is selected from the group consisting of:

15 -C(O)-R₁₀,
-C(O)O-R₉,
-C(O)-N(H)-R₁₀,
-S(O)₂-R₉,
-S(O)₂-NH-R₁₀,
-C(O)-CH₂-OR₁₀,
-C(O)C(O)-R₁₀;
20 -C(O)-CH₂N(R₁₀)(R₁₀),
-C(O)-CH₂C(O)-O-R₉,
-C(O)-CH₂C(O)-R₉,
-H, and
-C(O)-C(O)-OR₁₀;

25 each R₉ is independently selected from the group
consisting of -Ar₃ and a -C₁₋₆ straight or branched
alkyl group optionally substituted with Ar₃, wherein
the -C₁₋₆ alkyl group is optionally unsaturated;

30 each R₁₀ is independently selected from the group
consisting of -H, -Ar₃, a C₃₋₆ cycloalkyl group, and a
-C₁₋₆ straight or branched alkyl group optionally
substituted with Ar₃, wherein the -C₁₋₆ alkyl group is

- 156 -

optionally unsaturated;

5 R_{13} is selected from the group consisting of H, Ar_3 , and a C_{1-6} straight or branched alkyl group optionally substituted with Ar_3 , $-CONH_2$, $-OR_5$, $-OH$, $-OR_9$, or $-CO_2H$;

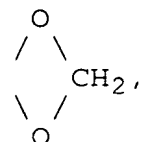
each R_{21} is independently selected from the group consisting of $-H$ or a $-C_{1-6}$ straight or branched alkyl group;

10 each R_{51} is independently selected from the group consisting of R_9 , $-C(O)-R_9$, $-C(O)-N(H)-R_9$, or each R_{51} taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing $-O-$, $-S-$, or $-NH-$;

15 each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from $-O-$, $-S-$, $-SO-$, SO_2 , $=N-$, and $-NH-$,
20 said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

25 each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, $-Cl$, $-F$, $-Br$, $-I$, $-NO_2$, $-CN$, $=O$, $-OH$, $-perfluoro\ C_{1-3}\ alkyl$, R_5 , $-OR_5$, $-NHR_5$, OR_9 , $-N(R_9)(R_{10})$, R_9 , $-C(O)-R_{10}$, and

30



- 157 -

provided that when $-\text{Ar}_3$ is substituted with a Q_1 group which comprises one or more additional $-\text{Ar}_3$ groups, said additional $-\text{Ar}_3$ groups are not substituted with another $-\text{Ar}_3$.

Preferred compounds of embodiment F employ formula (III), wherein R_1 is (w2) and the other substituents are as defined above.

Preferably, when R_1 is (w2):

m is 1;

ring C is benzo, pyrido, or thieno;

R_5 is selected from the group consisting of:

- C(O)- R_{10} , wherein R_{10} is $-\text{Ar}_3$;
- C(O)O- R_9 , wherein R_9 is $-\text{CH}_2-\text{Ar}_3$;
- C(O)C(O)- R_{10} , wherein R_{10} is $-\text{Ar}_3$;
- R_9 , wherein R_9 is a C_{1-2} alkyl group substituted with $-\text{Ar}_3$; and
- C(O)C(O)-OR₁₀, wherein R_{10} is $-\text{CH}_2\text{Ar}_3$;

R_6 is H;

R_8 is selected from the group consisting $-\text{C(O)}-\text{R}_{10}$, $-\text{C(O)}-\text{CH}_2-\text{OR}_{10}$, and $-\text{C(O)}\text{CH}_2-\text{N}(\text{R}_{10})(\text{R}_{10})$, wherein R_{10} is H, CH_3 , or $-\text{CH}_2\text{CH}_3$;

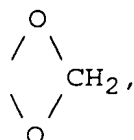
R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with Ar_3 , $-\text{OH}$, $-\text{OR}_9$, $-\text{CO}_2\text{H}$, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1 ;

- 158 -

Ar₃ is phenyl, naphthyl, thienyl, quinolinyl,
isoquinolinyl, thiazolyl, benzimidazolyl,
thienothienyl, thiadiazolyl, benzotriazolyl,
5 benzo[b]thiophenyl, benzofuranyl, and indolyl;

each Q₁ is independently selected from the group
consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅
wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is
-C(O)-R₁₀, -OR₉, -NHR₉, and

10



15 wherein each R₉ and R₁₀ are independently a -C₁₋₆
straight or branched alkyl group optionally substituted
with Ar₃ wherein Ar₃ is phenyl;

20 provided that when -Ar₃ is substituted with a Q₁
group which comprises one or more additional -Ar₃
groups, said additional -Ar₃ groups are not substituted
with another -Ar₃.

25 Other preferred compounds of embodiment F employ
formula (III), wherein R₁ is (e11) and the other
substituents are as defined above.

Other preferred compounds of embodiment F employ
formula (III), wherein R₁ is (e12) and the other
substituents are as defined above.

30 Other preferred compounds of embodiment F employ
formula (III), wherein R₁ is (y1) and the other
substituents are as defined above.

- 159 -

Other preferred compounds of embodiment F employ formula (III), wherein R_1 is (y2) and the other substituents are as defined above.

5 Other preferred compounds of embodiment F employ formula (III), wherein R_1 is (z) and the other substituents are as defined above.

10 Other preferred compounds of embodiment F employ formula (III), wherein R_1 is (e10) and X_5 is CH (also referred to herein as e10-B), and the other substituents are as defined above.

Other preferred compounds of embodiment F employ formula (III), wherein R_1 is (e10) and X_5 is N, (also referred to herein as e10-A) and the other substituents are as defined above.

15 Preferably, when R_1 is (e11), (e12), (y1), (y2), (z), (e10-A), and (e10-B), R_5 is selected from the group consisting of:

20 -C(O)- R_{10} ,
-C(O)O- R_9 , and
-C(O)-NH- R_{10} .

Alternatively, when R_1 is (e11), (e12), (y1), (y2), (z), (e10-A), and (e10-B), R_5 is selected from the group consisting of:

25 -S(O)₂- R_9 ,
-S(O)₂-NH- R_{10} ,
-C(O)-C(O)- R_{10} ,
- R_9 ,
-C(O)-C(O)-OR₁₀, and
-C(O)C(O)-N(R_9)(R_{10}).

30 More preferably, R_5 is R-C(O)-C(O)- R_{10} .

- 160 -

Alternatively, R_5 is $-C(O)-C(O)-OR_{10}$.

More preferably when R_1 is (e11), (e12), (y1), (y2), (z), (e10-A), and (e10-B):

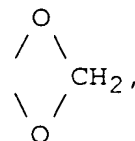
m is 1;

5 R_{21} is $-H$ or $-CH_3$;

R_{51} is a C_{1-6} straight or branched alkyl group optionally substituted with Ar_3 , wherein the Ar_3 cyclic group is phenyl, said cyclic group optionally being multiply or singly substituted by $-Q_1$;

10 each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl,
15 benzo[b]thiophenyl, pyridyl, benzofuranyl, or indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-Cl$, $-F$, $-Br$, $-OH$, $-R_9$, $-NH-R_5$
20 wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-N(R_9)(R_{10})$, and



25

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted
30 with Ar_3 , wherein the Ar_3 cyclic group is phenyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

- 161 -

provided that when $-Ar_3$ is substituted with a $-Q_1$ group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

More preferably, in these more preferred compounds, the Ar_3 cyclic group is selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$.

Compounds in a preferred form of this embodiment F are those wherein:

R_5 is $-C(O)-R_{10}$, wherein:

R_{10} is Ar_3 , wherein the Ar_3 cyclic group is phenyl, said cyclic group optionally being singly or multiply substituted by:

$-F$,

$-Cl$,

$-N(H)-R_5$, wherein $-R_5$ is $-H$ or $-C(O)-R_{10}$, wherein R_{10} is a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 , wherein the Ar_3 cyclic group is phenyl, said cyclic group optionally being singly or multiply substituted by $-Q_1$,

$-N(R_9)(R_{10})$, wherein R_9 and R_{10} are independently a $-C_{1-4}$ straight or branched alkyl group, or

$-O-R_5$, wherein R_5 is H or a $-C_{1-4}$ straight or branched alkyl group.

- 162 -

More preferably the Ar₃ cyclic group is phenyl optionally being singly or multiply substituted at the 3- or 5-position by -Cl or at the 4-position by -NH-R₅, -N(R₉)(R₁₀), or -O-R₅.

5 Other preferred compounds of embodiment F include those wherein R₅ is -C(O)-R₁₀, wherein R₁₀ is Ar₃ and the Ar₃ cyclic group is selected from the group consisting of indolyl, benzimidazolyl, thienyl, and benzo[b]thiophenyl, and said cyclic group optionally
10 being singly or multiply substituted by -Q₁;

Other preferred compounds of embodiment F include those wherein R₅ is -C(O)-R₁₀, wherein R₁₀ is Ar₃ and the Ar₃ cyclic group is selected from quinolyl and isoquinolyl, and said cyclic group optionally being
15 singly or multiply substituted by -Q₁.

Other preferred compounds of embodiment F are those wherein R₅ is -C(O)-R₁₀, wherein R₁₀ is Ar₃, wherein the Ar₃ cyclic group is phenyl, substituted by



25 In another form of embodiment F the compounds are as described above, further provided that when:

m is 1;
R₁ is (e10);
X₅ is CH;
R₁₅ is -OH;
30 R₂₁ is -H; and

- 163 -

Y_2 is O and R_3 is $-C(O)-H$, then R_5 cannot be:

$-C(O)-R_{10}$, wherein R_{10} is $-Ar_3$ and the Ar_3 cyclic group is phenyl, unsubstituted by $-Q_1$, 4-

(carboxymethoxy)phenyl, 2-fluorophenyl, 2-pyridyl, N-
5 (4-methylpiperazino)methylphenyl, or

$-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$, and the Ar_3 cyclic group is phenyl, unsubstituted by $-Q_1$,; and when

Y_2 is O, R_3 is $-C(O)-CH_2-T_1-R_{11}$, T_1 is O, and R_{11} is Ar_4 , wherein the Ar_4 cyclic group is 5-(1-(4-chlorophenyl)-3-trifluoromethyl)pyrazolyl), then R_5
10 cannot be:

$-C(O)-R_{10}$, wherein R_{10} is $-Ar_3$ and the Ar_3 cyclic group is 4-(dimethylaminomethyl)phenyl, phenyl, 4-(carboxymethylthio)phenyl, 4-(carboxyethylthio)phenyl,
15 4-(carboxyethyl)phenyl, 4-(carboxypropyl)phenyl, 2-fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

$-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$ and the Ar_3 cyclic group is phenyl;

20 and when R_{11} is Ar_4 , wherein the Ar_4 cyclic group is 5-(1-phenyl-3-trifluoromethyl)pyrazolyl), then R_5 cannot be:

$-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$, and the Ar_3 cyclic group is phenyl;

25 and when R_{11} is Ar_4 , wherein the Ar_4 cyclic group is 5-(1-(2-pyridyl)-3-trifluoromethyl)pyrazolyl), then R_5 cannot be:

$-C(O)-R_{10}$, wherein R_{10} is $-Ar_3$ and the Ar_3 cyclic group is 4-(dimethylaminomethyl)phenyl, or

30 $-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$, and the Ar_3 cyclic group is phenyl, unsubstituted by $-Q_1$,; and when

Y_2 is O, R_3 is $-C(O)-CH_2-T_1-R_{11}$, T_1 is O, and R_{11} is $-C(O)-Ar_4$, wherein the Ar_4 cyclic group is 2,5-

- 164 -

dichlorophenyl, then R_5 cannot be:

-C(O)- R_{10} , wherein R_{10} is - Ar_3 and the Ar_3 cyclic group is 4-(dimethylaminomethyl)phenyl, 4-(N-morpholinomethyl)phenyl, 4-(N-methylpiperazino)methyl)phenyl, 4-(N-(2-methyl)imidazolylmethyl)phenyl, 5-benzimidazolyl, 5-benzotriazolyl, N-carboethoxy-5-benzotriazolyl, N-carboethoxy-5-benzimidazolyl, or
 10 -C(O)- OR_9 , wherein R_9 is - CH_2-Ar_3 , and the Ar_3 cyclic group is phenyl, unsubstituted by - Q_1 ,; and when

Y_2 is H_2 , R_3 is -C(O)- $CH_2-T_1-R_{11}$, T_1 is O, and R_{11} is
 -C(O)- Ar_4 , wherein the Ar_4 cyclic group is 2,5-dichlorophenyl, then R_5 cannot be:
 15 -C(O)- OR_9 , wherein R_9 is - CH_2-Ar_3 and the Ar_3 cyclic group is phenyl.

In another form of embodiment F, preferred compounds are those wherein R_{21} is -H.

Alternatively, preferred compounds are those
 20 wherein R_{21} is - CH_3 .

Preferred compounds of embodiment F employ formula (III), wherein R_1 is (w2) and the other substituents are as defined above.

More preferably, R_1 is (w2) and

25 m is 1;

ring C is benzo, pyrido, or thieno;

R_3 is selected from the group consisting of -C(O)-H, -C(O)- Ar_2 , and -C(O) $CH_2-T_1-R_{11}$;

- 165 -

R₅ is selected from the group consisting of:

-C(O)-R₁₀, wherein R₁₀ is -Ar₃;

-C(O)O-R₉, wherein R₉ is -CH₂-Ar₃;

-C(O)C(O)-R₁₀, wherein R₁₀ is -Ar₃;

5 -R₉, wherein R₉ is a C₁₋₂ alkyl group
substituted with -Ar₃; and

-C(O)C(O)-OR₁₀, wherein R₁₀ is -CH₂Ar₃;

T₁ is O or S;

10 R₆ is H;

R₈ is selected from the group consisting -C(O)-R₁₀,
-C(O)-CH₂-OR₁₀, and -C(O)CH₂-N(R₁₀)(R₁₀), wherein R₁₀ is
H, CH₃, or -CH₂CH₃;

15 R₁₁ is selected from the group consisting of -Ar₄,
-(CH₂)₁₋₃-Ar₄, and -C(O)-Ar₄;

20 R₁₅ is -OH or -OC₁₋₄ straight or branched alkyl
group optionally substituted with -Ar₃, -OH, -OR₉, or
-CO₂H, wherein the R₉ is a -C₁₋₄ branched or straight
alkyl group, wherein Ar₃ is morpholinyl or phenyl,
wherein the phenyl is optionally substituted with Q₁;

Ar₂ is (hh);

Y is O;

25 each Ar₃ cyclic group is independently selected
from the set consisting of phenyl, naphthyl, thienyl,
quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl,
thienothienyl, thiadiazolyl, benzotriazolyl,
benzo[b]thiophenyl, benzofuranyl, and indolyl, and said
cyclic group optionally being singly or multiply
30 substituted by -Q₁;

- 166 -

each Ar₄ cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, naphthyl, pyridinyl, oxazolyl, pyrimidinyl, or indolyl, said cyclic group optionally being singly or multiply substituted by -Q₁;

each Q₁ is independently selected from the group consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅ wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is -C(O)-R₁₀, -OR₉, -N(R₉)(R₁₀), and



15 wherein each R₉ and R₁₀ are independently a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃ wherein Ar₃ is phenyl;

20 provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃.

25 Other preferred compounds of embodiment F employ formula (III), wherein R₁ is (e11) and the other substituents are as defined above.

Other preferred compounds of embodiment F employ formula (III), wherein R₁ is (e12) and the other substituents are as defined above.

30 Other preferred compounds of embodiment F employ formula (III) wherein R₁ is (y1) and the other substituents are as defined above.

- 167 -

Other preferred compounds of embodiment F employ formula (III) wherein R_1 is (y2) and the other substituents are as defined above.

5 Other preferred compounds of embodiment F of employ formula (III) wherein R_1 is (z) and the other substituents are as defined above.

Other preferred compounds of embodiment F employ formula (III) wherein R_1 is (e10), X_5 is CH, and the other substituents are as defined above.

10 Other preferred compounds of embodiment F employ formula (III) wherein R_1 is (e10), X_5 is N, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R_5 is selected from the group consisting of:

15 -C(O)- R_{10} ,
 -C(O)O- R_9 , and
 -C(O)-NH- R_{10} .

Alternatively, in these more preferred compounds, R_5 is selected from the group consisting of:

20 -S(O)₂- R_9 ,
 -S(O)₂-NH- R_{10} ,
 -C(O)-C(O)- R_{10} ,
 - R_9 ,
 -C(O)-C(O)-OR₁₀, and
25 -C(O)C(O)-N(R_9)(R_{10}).

Most preferably, in these more preferred compounds,

m is 1;

R_{13} is H or a -C₁₋₄ straight or branched alkyl

- 168 -

group optionally substituted with $-\text{Ar}_3$, $-\text{OH}$, $-\text{OR}_9$, or $-\text{CO}_2\text{H}$, wherein the R_9 is a $-\text{C}_{1-4}$ branched or straight alkyl group, wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1 ;

5 R_{21} is $-\text{H}$ or $-\text{CH}_3$;

R_{51} is a C_{1-6} straight or branched alkyl group optionally substituted with Ar_3 , wherein Ar_3 is phenyl, optionally substituted by $-\text{Q}_1$;

10 each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl,
15 benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-\text{Q}_1$;

each Q_1 is independently selected from the group consisting of $-\text{NH}_2$, $-\text{Cl}$, $-\text{F}$, $-\text{Br}$, $-\text{OH}$, $-\text{R}_9$, $-\text{NH}-\text{R}_5$
20 wherein R_5 is $-\text{C}(\text{O})-\text{R}_{10}$ or $-\text{S}(\text{O})_2-\text{R}_9$, $-\text{OR}_5$ wherein R_5 is $-\text{C}(\text{O})-\text{R}_{10}$, $-\text{OR}_9$, $-\text{N}(\text{R}_9)(\text{R}_{10})$, and



wherein each R_9 and R_{10} are independently a $-\text{C}_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

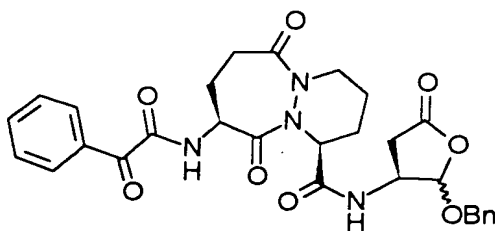
30 provided that when $-\text{Ar}_3$ is substituted with a Q_1 group which comprises one or more additional $-\text{Ar}_3$ groups, said additional $-\text{Ar}_3$ groups are not substituted

- 169 -

with another $-\text{Ar}_3$.

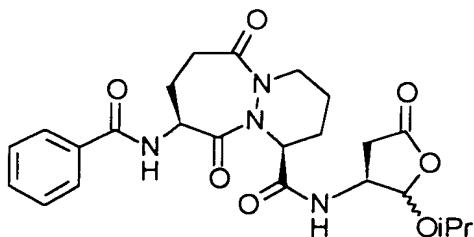
Preferred compounds of embodiment (F) include; but are not limited to:

2001

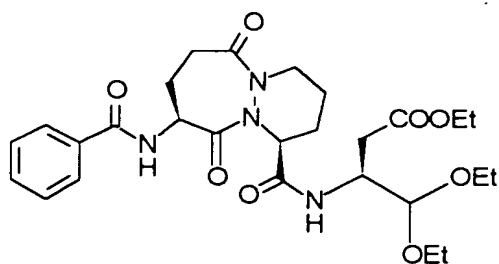


5

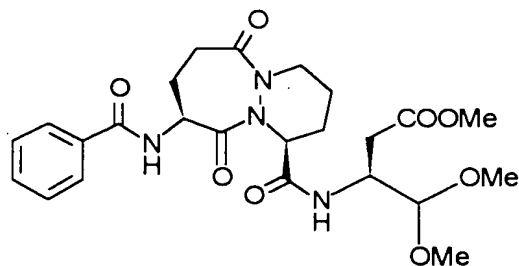
2100a



2100b

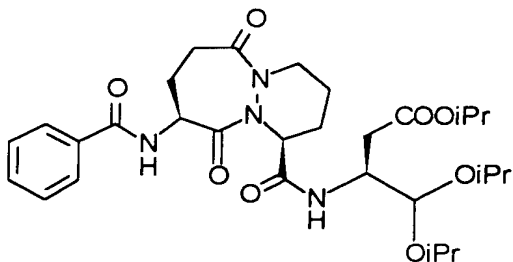


2100c

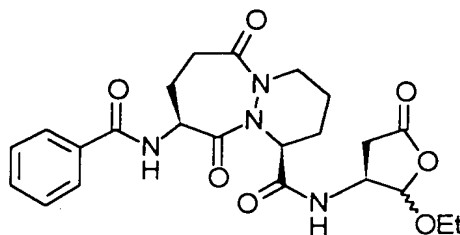


- 170 -

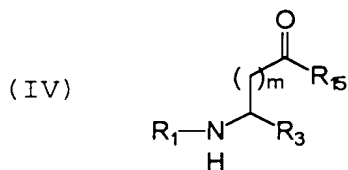
2100d



2100e



5 The ICE inhibitors of another embodiment (G)
of this invention are those of formula (IV):



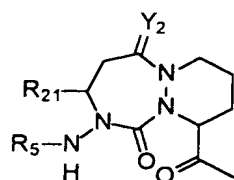
wherein:

m is 1 or 2;

10 R₁ is selected from the group consisting of the
following formulae:

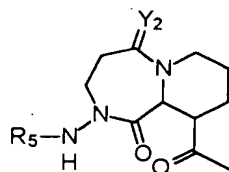
- 171 -

(e10-A)



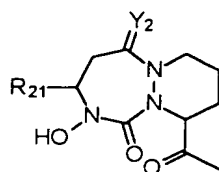
;

(e11)



;

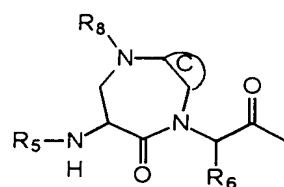
(e12)



;

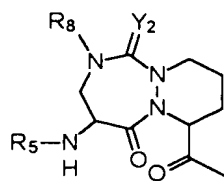
5

(w2)



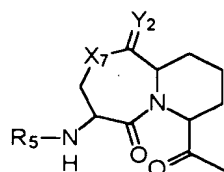
;

(y1)



;

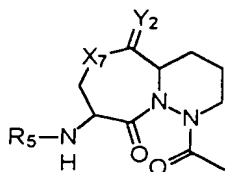
(y2)



;

- 172 -

(z)



; and

ring C is chosen from the group consisting of
benzo, pyrido, thieno, pyrrolo, furano, thiazolo,
5 isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo,
cyclopentyl, and cyclohexyl;

R_3 is selected from the group consisting of:

-CN,
-C(O)-H,
10 -C(O)-CH₂-T₁-R₁₁,
-C(O)-CH₂-F,
-C=N-O-R₉, and
-CO-Ar₂;

each R_5 is independently selected from the
15 group consisting of:

-C(O)-R₁₀,
-C(O)O-R₉,
-C(O)-N(R₁₀)(R₁₀)
-S(O)₂-R₉,
20 -S(O)₂-NH-R₁₀,
-C(O)-CH₂-O-R₉,
-C(O)C(O)-R₁₀,
-R₉,
-H,
25 -C(O)C(O)-OR₁₀, and
-C(O)C(O)-N(R₉)(R₁₀);

Y_2 is H₂ or O;

X_7 is -N(R₈)- or -O-;

- 173 -

each T_1 is independently selected from the group consisting of -O-, -S-, -S(O)-, and -S(O)₂-;

5 R_6 is selected from the group consisting of -H and -CH₃;

R_8 is selected from the group consisting of:

10 -C(O)-R₁₀,
-C(O)O-R₉,
-C(O)-NH-R₁₀,
-S(O)₂-R₉,
-S(O)₂-NH-R₁₀,
-C(O)-CH₂-OR₁₀,
-C(O)C(O)-R₁₀,
15 -C(O)-CH₂-N(R₁₀)(R₁₀),
-C(O)-CH₂C(O)-O-R₉,
-C(O)-CH₂C(O)-R₉,
-H, and
-C(O)-C(O)-OR₁₀;

20 each R_9 is independently selected from the group consisting of -Ar₃ and a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein the -C₁₋₆ alkyl group is optionally unsaturated;

25 each R_{10} is independently selected from the group consisting of -H, -Ar₃, a C₃₋₆ cycloalkyl group, and a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein the -C₁₋₆ alkyl group is optionally unsaturated;

30 each R_{11} is independently selected from the group consisting of:

-Ar₄,
-(CH₂)₁₋₃-Ar₄,
-H, and

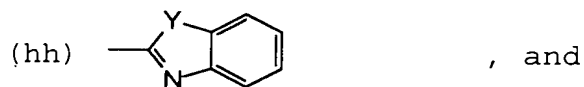
- 174 -

-C(O)-Ar₄;

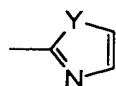
R₁₅ is selected from the group consisting of -OH, -OAr₃, -N(H)-OH, and -OC₁₋₆, wherein C₁₋₆ is a straight or branched alkyl group optionally substituted with
 5 Ar₃, -CONH₂, -OR₅, -OH, -OR₉, or -CO₂H;

each R₂₁ is independently selected from the group consisting of -H or a -C₁₋₆ straight or branched alkyl group;

Ar₂ is independently selected from the following
 10 group, in which any ring may optionally be singly or multiply substituted by -Q₁ or phenyl, optionally substituted by Q₁:



(ii)



15

wherein each Y is independently selected from the group consisting of O and S;

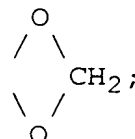
each Ar₃ is a cyclic group independently selected from the set consisting of an aryl group which contains
 20 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO₂, =N-, and -NH-,
 25 -N(R₅)-, and -N(R₉)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or

- 175 -

multiply substituted by $-Q_1$;

each Ar_4 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from $-O-$, $-S-$, $-SO-$, SO_2 , $=N-$, $-NH-$, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, $-Cl$, $-F$, $-Br$, $-I$, $-NO_2$, $-CN$, $=O$, $-OH$, $-perfluoro\ C_{1-3}\ alkyl$, R_5 , $-OR_5$, $-NHR_5$, OR_9 , $-N(R_9)(R_{10})$, R_9 , $-C(O)-R_{10}$, and



provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$;

Preferred compounds of embodiment G employ formula (IV), wherein R_1 is (w2) and the other substituents are as defined above.

Preferably, when R_1 is (w2):

m is 1;

- 176 -

ring C is benzo, pyrido, or thieno;

R₅ is selected from the group consisting of:

- C(O)-R₁₀, wherein R₁₀ is -Ar₃;
- C(O)O-R₉, wherein R₉ is -CH₂-Ar₃;
- 5 -C(O)C(O)-R₁₀, wherein R₁₀ is -Ar₃;
- R₉, wherein R₉ is a C₁₋₂ alkyl group substituted with -Ar₃; and
- C(O)C(O)-OR₁₀, wherein R₁₀ is -CH₂Ar₃;

10 R₆ is H;

R₈ is selected from the group consisting -C(O)-R₁₀, -C(O)-CH₂-OR₁₀, and -C(O)CH₂-N(R₁₀)(R₁₀), wherein R₁₀ is H, CH₃, or -CH₂CH₃;

15 R₁₃ is H or a C₁₋₄ straight or branched alkyl group optionally substituted with Ar₃, -OH, -OR₉, -CO₂H, wherein the R₉ is a C₁₋₄ branched or straight chain alkyl group; wherein Ar₃ is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q₁;

20 Ar₃ is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl;

25 each Q₁ is independently selected from the group consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅ wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is -C(O)-R₁₀, -OR₉, -NHR₉, and



- 177 -

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

5 provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

10 Other preferred compounds of embodiment G employ formula (IV) wherein R_1 is (e10-A) and the other substituents are as defined above.

Other preferred compounds of embodiment G employ formula (IV) wherein R_1 is (e11) and the other substituents are as defined above.

15 Other preferred compounds of embodiment G employ formula (IV) wherein R_1 is (e12) and the other substituents are as defined above.

20 Other preferred compounds of embodiment G employ formula (IV) wherein R_1 is (y1) and the other substituents are as defined above.

Other preferred compounds of embodiment G employ formula (IV) wherein R_1 is (y2) and the other substituents are as defined above.

25 Other preferred compounds of embodiment G employ formula (IV) wherein R_1 is (z) and the other substituents are as defined above.

More preferred compounds of embodiment G are those wherein R_3 is $-CO-Ar_2$.

- 178 -

Most preferably, when R_3 is $-\text{CO}-\text{Ar}_2$, Y is O .

Other more preferred compounds are those wherein R_3 is $-\text{C}(\text{O})-\text{CH}_2-\text{T}_1-\text{R}_{11}$ and R_{11} is $-(\text{CH}_2)_{1-3}-\text{Ar}_4$.

Most preferably, when R_3 is $-\text{C}(\text{O})-\text{CH}_2-\text{T}_1-\text{R}_{11}$ and R_{11} is $-(\text{CH}_2)_{1-3}-\text{Ar}_4$, T_1 is O .

Other more preferred compounds are those wherein:

R_3 is $-\text{C}(\text{O})-\text{CH}_2-\text{T}_1-\text{R}_{11}$;

T_1 is O ; and

R_{11} is $-\text{C}(\text{O})-\text{Ar}_4$.

Other more preferred compounds are those wherein R_3 is $-\text{C}(\text{O})-\text{H}$.

Other more preferred compounds are those wherein R_3 is $-\text{CO}-\text{CH}_2-\text{T}_1-\text{R}_{11}$ and R_{11} is $-\text{Ar}_4$.

More preferably, when R_3 is $-\text{CO}-\text{CH}_2-\text{T}_1-\text{R}_{11}$ and R_{11} is $-\text{Ar}_4$, T_1 is O or S .

More preferably, when R_1 is $(\text{e}11)$, $(\text{e}12)$, $(\text{y}1)$, $(\text{y}2)$, (z) , $(\text{e}10-\text{A})$, and $(\text{e}10-\text{B})$, R_5 is selected from the group consisting of:

$-\text{C}(\text{O})-\text{R}_{10}$,

$-\text{C}(\text{O})\text{O}-\text{R}_9$, and

$-\text{C}(\text{O})-\text{NH}-\text{R}_{10}$.

Alternatively, when R_1 is $(\text{e}11)$, $(\text{e}12)$, $(\text{y}1)$, $(\text{y}2)$, (z) , $(\text{e}10-\text{A})$, and $(\text{e}10-\text{B})$, R_5 is selected from the group consisting of:

$-\text{S}(\text{O})_2-\text{R}_9$,

$-\text{S}(\text{O})_2-\text{NH}-\text{R}_{10}$,

$-\text{C}(\text{O})-\text{C}(\text{O})-\text{R}_{10}$,

$-\text{R}_9$,

- 179 -

-C(O)-C(O)-OR₁₀, and
-C(O)-C(O)-N(R₉)(R₁₀).

More preferably, R₅ is -C(O)-C(O)-R₁₀.

Alternatively, R₅ is -C(O)-C(O)-OR₁₀.

5 Most preferably, when R₁ is (e11), (e12), (y1), (y2),
(z), (e10-A), and (e10-B),:

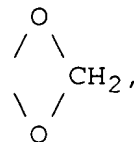
m is 1;

R₂₁ is -H or -CH₃;

10 R₅₁ is a C₁₋₆ straight or branched alkyl group
optionally substituted with Ar₃, wherein the Ar₃ cyclic
group is phenyl, said cyclic group optionally being
multiply or singly substituted by -Q₁;

15 each Ar₃ cyclic group is independently selected
from the set consisting of phenyl, naphthyl, thienyl,
quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl,
isoxazolyl, benzotriazolyl, benzimidazolyl,
thienothienyl, imidazolyl, thiadiazolyl,
benzo[b]thiophenyl, pyridyl, benzofuranyl, or indolyl,
20 and said cyclic group optionally being singly or
multiply substituted by -Q₁;

25 each Q₁ is independently selected from the group
consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅
wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is
-C(O)-R₁₀, -OR₉, -N(R₉)(R₁₀), and



30

- 180 -

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 , wherein the Ar_3 cyclic group is phenyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

provided that when $-Ar_3$ is substituted with a $-Q_1$ group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

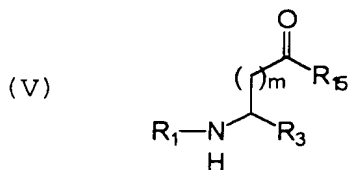
More preferably, in these more preferred compounds, the Ar_3 cyclic group is selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$.

Compounds in a preferred form of embodiment G are those wherein R_{21} is H and the other substituents are as defined above.

Compounds in another preferred form of embodiment G are those wherein R_{21} is CH_3 and the other substituents are as defined above.

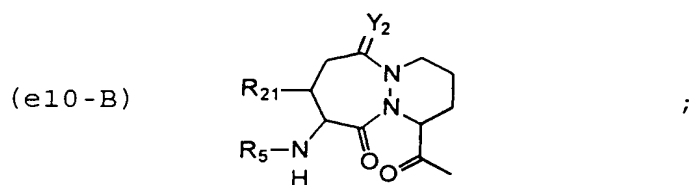
The ICE inhibitors of another embodiment (H) of this invention are those of formula (V):

- 181 -



wherein:

m is 1 or 2;

5 R₁ is:R₃ is selected from the group consisting of:

- 10 -CN,
 -C(O)-H,
 -C(O)-CH₂-T₁-R₁₁,
 -C(O)-CH₂-F,
 -C=N-O-R₉, and
 -CO-Ar₂;

15 each R₅ is independently selected from the group
 consisting of:

- 20 -C(O)-R₁₀,
 -C(O)O-R₉,
 -C(O)-N(R₁₀)(R₁₀)
 -S(O)₂-R₉,
 -S(O)₂-NH-R₁₀,
 -C(O)-CH₂-O-R₉,
 -C(O)C(O)-R₁₀,
 -R₉,
 -H, and

25 -C(O)C(O)-N(R₉)(R₁₀), and
 -C(O)C(O)-OR₁₀;

- 182 -

Y_2 is H_2 or O;

each T_1 is independently selected from the group consisting of -O-, -S-, -S(O)-, and -S(O)₂-;

5 R_8 is selected from the group consisting of:

-C(O)- R_{10} ,
-C(O)O- R_9 ,
-C(O)-NH- R_{10} ,
-S(O)₂- R_9 ,
10 -S(O)₂-NH- R_{10} ,
-C(O)-CH₂-OR₁₀,
-C(O)C(O)- R_{10} ,
-C(O)-CH₂-N(R_{10})(R_{10}),
-C(O)-CH₂C(O)-O- R_9 ,
15 -C(O)-CH₂C(O)- R_9 ,
-H, and
-C(O)-C(O)-OR₁₀;

each R_9 is independently selected from the group consisting of -Ar₃ and a -C₁₋₆ straight or branched
20 alkyl group optionally substituted with Ar₃, wherein the -C₁₋₆ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, -Ar₃, a C₃₋₆ cycloalkyl group, and a
-C₁₋₆ straight or branched alkyl group optionally
25 substituted with Ar₃, wherein the -C₁₋₆ alkyl group is optionally unsaturated;

each R_{11} is independently selected from the group consisting of:

-Ar₄,
30 -(CH₂)₁₋₃-Ar₄,
-H, and
-C(O)-Ar₄;

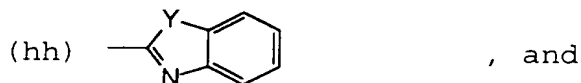
- 183 -

R₁₅ is selected from the group consisting of -OH, -OAr₃, -N(H)-OH, and -OC₁₋₆, wherein C₁₋₆ is a straight or branched alkyl group optionally substituted with Ar₃,

5 -CONH₂, -OR₅, -OH, -OR₉, or -CO₂H;

R₂₁ is -CH₃;

Ar₂ is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q₁ or phenyl, optionally substituted by Q₁:



15 wherein each Y is independently selected from the group consisting of O and S;

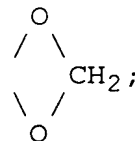
each Ar₃ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO₂, =N-, and -NH-, -N(R₅)-, and -N(R₉)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q₁;

each Ar₄ is a cyclic group independently selected

- 184 -

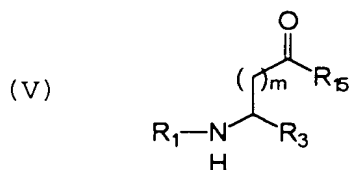
from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said
 5 heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO₂, =N-, -NH-, -N(R₅)-, and -N(R₉)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings,
 10 and said cyclic group optionally being singly or multiply substituted by -Q₁;

each Q₁ is independently selected from the group consisting of -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH, -perfluoro C₁₋₃ alkyl, R₅, -OR₅, -NHR₅, OR₉,
 15 -N(R₉)(R₁₀), R₉, -C(O)-R₁₀, and



20 provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃ groups, said additional -Ar₃ groups are not substituted with another -Ar₃;

Compounds of another form of embodiment (I)
 25 (form 1) are those of formula (V):



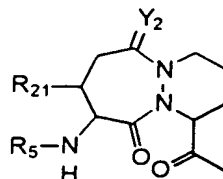
wherein:

m is 1 or 2;

- 185 -

R₁ is:

(e10-B)



;

R₃ is selected from the group consisting of:

- CN,
- C(O)-H,
- C(O)-CH₂-T₁-R₁₁,
- C(O)-CH₂-F,
- C=N-O-R₉, and
- CO-Ar₂;

each R₅ is -C(O)C(O)-OR₁₀;Y₂ is H₂ or O;each T₁ is independently selected from the group consisting of -O-, -S-, -S(O)-, and -S(O)₂-;R₈ is selected from the group consisting of:

- C(O)-R₁₀,
- C(O)O-R₉,
- C(O)-NH-R₁₀,
- S(O)₂-R₉,
- S(O)₂-NH-R₁₀,
- C(O)-CH₂-OR₁₀,
- C(O)C(O)-R₁₀,
- C(O)-CH₂-N(R₁₀)(R₁₀),
- C(O)-CH₂C(O)-O-R₉,
- C(O)-CH₂C(O)-R₉,
- H, and
- C(O)-C(O)-OR₁₀;

- 186 -

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 , wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

5 each R_{10} is independently selected from the group consisting of $-H$, $-Ar_3$, a C_{3-6} cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 , wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

10 each R_{11} is independently selected from the group consisting of:

$-Ar_4$,
 $-(CH_2)_{1-3}-Ar_4$,
 $-H$, and

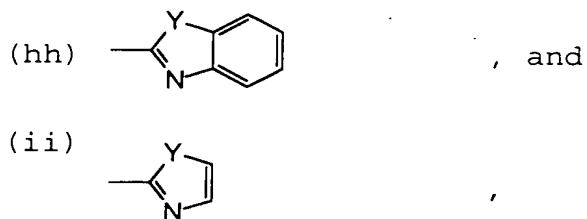
15 $-C(O)-Ar_4$;

R_{15} is selected from the group consisting of $-OH$, $-OAr_3$, $-N(H)-OH$, and $-OC_{1-6}$, wherein C_{1-6} is a straight or branched alkyl group optionally substituted with Ar_3 , $-CONH_2$, $-OR_5$, $-OH$, $-OR_9$, or $-CO_2H$;

20 each R_{21} is independently selected from the group consisting of $-H$ or a $-C_{1-6}$ straight or branched alkyl group;

25 Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by $-Q_1$ or phenyl, optionally substituted by Q_1 :

- 187 -



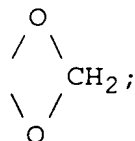
wherein each Y is independently selected from the
 5 group consisting of O and S;

each Ar₃ is a cyclic group independently selected
 from the set consisting of an aryl group which contains
 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings
 and an aromatic heterocycle group containing between 5
 10 and 15 ring atoms and between 1 and 3 rings, said
 heterocyclic group containing at least one heteroatom
 group selected from -O-, -S-, -SO-, SO₂, =N-, and -NH-,
 -N(R₅)-, and -N(R₉)- said heterocycle group optionally
 containing one or more double bonds, said heterocycle
 15 group optionally comprising one or more aromatic rings,
 and said cyclic group optionally being singly or
 multiply substituted by -Q₁;

each Ar₄ is a cyclic group independently selected
 from the set consisting of an aryl group which contains
 20 6, 10, 12, or 14 carbon atoms and between 1 and 3
 rings, and a heterocycle group containing between 5 and
 15 ring atoms and between 1 and 3 rings, said
 heterocyclic group containing at least one heteroatom
 group selected from -O-, -S-, -SO-, SO₂, =N-, -NH-,
 25 -N(R₅)-, and -N(R₉)- said heterocycle group optionally
 containing one or more double bonds, said heterocycle
 group optionally comprising one or more aromatic rings,
 and said cyclic group optionally being singly or
 multiply substituted by -Q₁;

30 each Q₁ is independently selected from the group

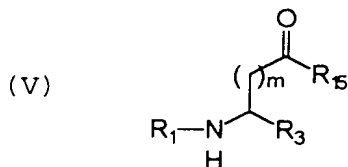
consisting of -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH, -perfluoro C₁₋₃ alkyl, R₅, -OR₅, -NHR₅, OR₉, -N(R₉)(R₁₀), R₉, -C(O)-R₁₀, and O



provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$;

Alternatively, compounds of this form of embodiment I (form 2) are those wherein R_{21} is $-CH_3$.

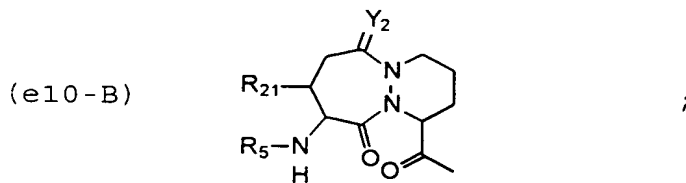
Compounds of another form of embodiment (J) (form
15 1) are those of formula (V):



wherein:

m is 1 or 2;

20 R_1 is:



R_3 is selected from the group consisting of:

$$-\text{CN},$$
$$-\text{C}(\text{O})-\text{H},$$

- 189 -

-C(O)-CH₂-T₁-R₁₁,
 -C(O)-CH₂-F,
 -C=N-O-R₉, and
 -CO-Ar₂;

5 each R₅ is independently selected from the
 group consisting of:

 -C(O)-R₁₀,
 -C(O)O-R₉,
 -C(O)-N(R₁₀)(R₁₀)
 10 -S(O)₂-R₉,
 -S(O)₂-NH-R₁₀,
 -C(O)-CH₂-O-R₉,
 -C(O)C(O)-R₁₀,
 -R₉,
 15 -H,
 -C(O)C(O)-OR₁₀, and
 -C(O)C(O)-N(R₉)(R₁₀);

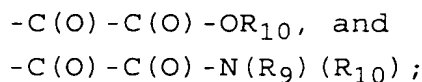
Y₂ is H₂ or O;

20 each T₁ is independently selected from the group
 consisting of -O-, -S-, -S(O)-, and -S(O)₂-;

R₈ is selected from the group consisting of:

 -C(O)-R₁₀,
 -C(O)O-R₉,
 25 -C(O)-NH-R₁₀,
 -S(O)₂-R₉,
 -S(O)₂-NH-R₁₀,
 -C(O)-CH₂-OR₁₀,
 -C(O)C(O)-R₁₀,
 30 -C(O)-CH₂-N(R₁₀)(R₁₀),
 -C(O)-CH₂C(O)-O-R₉,
 -C(O)-CH₂C(O)-R₉,
 -H,

- 190 -



5 each R_9 is independently selected from the group consisting of $-\text{Ar}_3$ and a $-\text{C}_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 , wherein the $-\text{C}_{1-6}$ alkyl group is optionally unsaturated;

10 each R_{10} is independently selected from the group consisting of $-\text{H}$, $-\text{Ar}_3$, a C_{3-6} cycloalkyl group, and a $-\text{C}_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 , wherein the $-\text{C}_{1-6}$ alkyl group is optionally unsaturated;

each R_{11} is independently selected from the group consisting of:

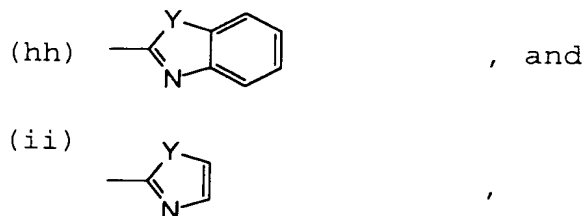
15 $-\text{Ar}_4$,
 $-(\text{CH}_2)_{1-3}-\text{Ar}_4$,
 $-\text{H}$, and
 $-\text{C}(\text{O})-\text{Ar}_4$;

20 R_{15} is selected from the group consisting of $-\text{OH}$, $-\text{OAr}_3$, $-\text{N}(\text{H})-\text{OH}$, and $-\text{OC}_{1-6}$, wherein C_{1-6} is a straight or branched alkyl group optionally substituted with Ar_3 ,
 $-\text{CONH}_2$, $-\text{OR}_5$, $-\text{OH}$, $-\text{OR}_9$, or $-\text{CO}_2\text{H}$;

25 each R_{21} is independently selected from the group consisting of $-\text{H}$ or a $-\text{C}_{1-6}$ straight or branched alkyl group;

Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by $-\text{Q}_1$ or phenyl, optionally substituted by Q_i :

- 191 -



5 wherein each Y is independently selected from the group consisting of O and S;

each Ar₃ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO₂, =N-, and -NH-, -N(R₅)-, and -N(R₉)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q₁;

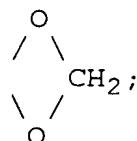
each Ar₄ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO₂, =N-, -NH-, -N(R₅)-, and -N(R₉)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q₁;

30 each Q₁ is independently selected from the group

- 192 -

consisting of $-NH_2$, $-CO_2H$, $-Cl$, $-F$, $-Br$, $-I$, $-NO_2$, $-CN$,
 $=O$, $-OH$, $-perfluoro\ C_{1-3}\ alkyl$, R_5 , $-OR_5$, $-NHR_5$, OR_9 ,
 $-N(R_9)(R_{10})$, R_9 , $-C(O)-R_{10}$, and

5



provided that when $-Ar_3$ is substituted with a Q_1
 group which comprises one or more additional $-Ar_3$
 10 groups, said additional $-Ar_3$ groups are not substituted
 with another $-Ar_3$;

provided that when:

m is 1;
 R_1 is (e10);
 15 X_5 is CH ;
 R_{15} is $-OH$;
 R_{21} is $-H$; and

Y_2 is O and R_3 is $-C(O)-H$, then R_5 cannot be:
 $-C(O)-R_{10}$, wherein R_{10} is $-Ar_3$ and the Ar_3 cyclic
 20 group is phenyl, unsubstituted by $-Q_1$, 4-
 (carboxymethoxy)phenyl, 2-fluorophenyl, 2-pyridyl, N-
 (4-methylpiperazino)methylphenyl, or
 $-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$, and the Ar_3
 cyclic group is phenyl, unsubstituted by $-Q_1$; and when

25 Y_2 is O , R_3 is $-C(O)-CH_2-T_1-R_{11}$, T_1 is O , and R_{11}
 is Ar_4 , wherein the Ar_4 cyclic group is 5-(1-(4-
 chlorophenyl)-3-trifluoromethyl)pyrazolyl), then R_5
 cannot be:

30 $-C(O)-R_{10}$, wherein R_{10} is $-Ar_3$ and the Ar_3 cyclic
 group is 4-(dimethylaminomethyl)phenyl, phenyl, 4-
 (carboxymethylthio)phenyl, 4-(carboxyethylthio)phenyl,
 4-(carboxyethyl)phenyl, 4-(carboxypropyl)phenyl, 2-

- 193 -

fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

-C(O)-OR₉, wherein R₉ is -CH₂-Ar₃ and the Ar₃ cyclic group is phenyl;

5 and when R₁₁ is Ar₄, wherein the Ar₄ cyclic group is 5-(1-phenyl-3-trifluoromethyl)pyrazolyl), then R₅ cannot be:

-C(O)-OR₉, wherein R₉ is -CH₂-Ar₃, and the Ar₃ cyclic group is phenyl;

10 and when R₁₁ is Ar₄, wherein the Ar₄ cyclic group is 5-(1-(2-pyridyl)-3-trifluoromethyl)pyrazolyl), then R₅ cannot be:

-C(O)-R₁₀, wherein R₁₀ is -Ar₃ and the Ar₃ cyclic group is 4-(dimethylaminomethyl)phenyl, or

15 -C(O)-OR₉, wherein R₉ is -CH₂-Ar₃, and the Ar₃ cyclic group is phenyl, unsubstituted by -Q₁,; and when

Y₂ is O, R₃ is -C(O)-CH₂-T₁-R₁₁, T₁ is O, and R₁₁ is -C(O)-Ar₄, wherein the Ar₄ cyclic group is 2,5-dichlorophenyl, then R₅ cannot be:

20 -C(O)-R₁₀, wherein R₁₀ is -Ar₃ and the Ar₃ cyclic group is 4-(dimethylaminomethyl)phenyl, 4-(N-morpholinomethyl)phenyl, 4-(N-methylpiperazino)methyl)phenyl, 4-(N-(2-methyl)imidazolylmethyl)phenyl, 5-benzimidazolyl, 5-benztriazolyl, N-carboethoxy-5-benztriazolyl, N-carboethoxy-5-benzimidazolyl, or

25 -C(O)-OR₉, wherein R₉ is -CH₂-Ar₃, and the Ar₃ cyclic group is phenyl, unsubstituted by -Q₁,; and when

30 Y₂ is H₂, R₃ is -C(O)-CH₂-T₁-R₁₁, T₁ is O, and R₁₁ is -C(O)-Ar₄, wherein the Ar₄ cyclic group is 2,5-dichlorophenyl, then R₅ cannot be:

-C(O)-OR₉, wherein R₉ is -CH₂-Ar₃ and the Ar₃

- 194 -

cyclic group is phenyl.

Compounds of another form of embodiment J (form 2) are those wherein R_{21} is $-\text{CH}_3$.

5 Compounds of another form of embodiment J (form 3) are those wherein R_5 is $-\text{C}(\text{O})-\text{C}(\text{O})-\text{OR}_{10}$.

Compounds of another form of embodiment J (form 4) are those wherein R_5 is $-\text{C}(\text{O})-\text{C}(\text{O})-\text{OR}_{10}$ and R_{21} is $-\text{CH}_3$.

Preferred compounds of embodiments H, I, and J employ formula (V), wherein R_3 is $-\text{CO}-\text{Ar}_2$.

10 More preferably, when R_3 is $-\text{CO}-\text{Ar}_2$ Y is O.

Preferred compounds of embodiments H, I, and J employ formula (V), wherein R_3 is $-\text{C}(\text{O})-\text{CH}_2-\text{T}_1-\text{R}_{11}$ and R_{11} is $-(\text{CH}_2)_{1-3}-\text{Ar}_4$.

15 More preferably, when R_3 is $-\text{C}(\text{O})-\text{CH}_2-\text{T}_1-\text{R}_{11}$ and R_{11} is $-(\text{CH}_2)_{1-3}-\text{Ar}_4$, T_1 is O.

Preferred compounds of embodiments H, I, and J employ formula (V), wherein R_3 is $-\text{C}(\text{O})-\text{CH}_2-\text{T}_1-\text{R}_{11}$, T_1 is O, and R_{11} is $-\text{C}(\text{O})-\text{Ar}_4$.

20 Preferred compounds of embodiments H, I, and J employ formula (V), wherein R_3 is $-\text{C}(\text{O})-\text{H}$.

Preferred compounds of embodiments H, I, and J employ formula (V), wherein R_3 is $-\text{CO}-\text{CH}_2-\text{T}_1-\text{R}_{11}$ and R_{11} is $-\text{Ar}_4$.

More preferably, when R_3 is $-\text{CO}-\text{CH}_2-\text{T}_1-\text{R}_{11}$ and

- 195 -

R_{11} is $-\text{Ar}_4$, T_1 is O or S.

More preferred compounds of embodiments H and J (forms 1 and 2) are those wherein R_5 is selected from the group consisting of:

- 5 $-\text{C}(\text{O})-\text{R}_{10}$,
 $-\text{C}(\text{O})\text{O}-\text{R}_9$, and
 $-\text{C}(\text{O})-\text{NH}-\text{R}_{10}$.

Alternatively, more preferred compounds of embodiments H and J (forms 1 and 2) are those wherein R_5 is selected from the group consisting of:

- 10 $-\text{S}(\text{O})_2-\text{R}_9$,
 $-\text{S}(\text{O})_2-\text{NH}-\text{R}_{10}$,
 $-\text{C}(\text{O})-\text{C}(\text{O})-\text{R}_{10}$,
 $-\text{R}_9$,
15 $-\text{C}(\text{O})-\text{C}(\text{O})-\text{OR}_{10}$, and
 $-\text{C}(\text{O})-\text{C}(\text{O})-\text{N}(\text{R}_9)(\text{R}_{10})$.

Most preferably, R_5 is $-\text{C}(\text{O})-\text{C}(\text{O})-\text{R}_{10}$.

Alternatively, R_5 is $-\text{C}(\text{O})-\text{C}(\text{O})-\text{OR}_{10}$.

20

More preferred compounds of embodiments H, I (form 2), and J (forms 2 and 4) are those wherein:

25 m is 1;

25

Y_2 is O;

30 R_{15} is $-\text{OH}$ or $-\text{OC}_{1-4}$ straight or branched alkyl group optionally substituted with Ar_3 , $-\text{OH}$, $-\text{OR}_9$, $-\text{CO}_2\text{H}$, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1 ;

- 196 -

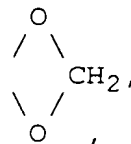
Ar₂ is (hh);

Y is O, and

5 each Ar₃ cyclic group is independently selected
from the set consisting of phenyl, naphthyl, thienyl,
quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl,
isoxazolyl, benzotriazolyl, benzimidazolyl,
thienothienyl, imidazolyl, thiadiazolyl,
10 benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl,
and said cyclic group optionally being singly or
multiply substituted by -Q₁;

15 each Ar₄ cyclic group is independently selected
from the group consisting of phenyl, tetrazolyl,
pyridyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl,
and said cyclic group optionally being singly or
multiply substituted by -Q₁;

20 each Q₁ is independently selected from the group
consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅
wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is
-C(O)-R₁₀, -OR₉, -N(R₉)(R₁₀), and



25

wherein each R₉ and R₁₀ are independently a -C₁₋₆
straight or branched alkyl group optionally substituted
with Ar₃ wherein the Ar₃ cyclic group is phenyl, and
said cyclic group optionally being singly or multiply
30 substituted by -Q₁;

provided that when -Ar₃ is substituted with a Q₁
group which comprises one or more additional -Ar₃
groups, said additional -Ar₃ groups are not substituted

- 197 -

with another $-Ar_3$.

More preferred compounds of embodiments I (form 1), and J (form 3) are those wherein:

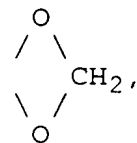
m is 1;

5 R_{21} is $-H$ or $-CH_3$;

R_{51} is a C_{1-6} straight or branched alkyl group optionally substituted with Ar_3 , wherein the Ar_3 cyclic group is phenyl, said cyclic group optionally being multiply or singly substituted by $-Q_1$;

10 each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinoliny, isoquinoliny, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl,
15 benzo[b]thiophenyl, pyridyl, benzofuranyl, or indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-Cl$, $-F$, $-Br$, $-OH$, $-R_9$, $-NH-R_5$
20 wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-N(R_9)(R_{10})$, and



25

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 , wherein the Ar_3 cyclic group is phenyl, and
30 said cyclic group optionally being singly or multiply substituted by $-Q_1$;

- 198 -

provided that when $-Ar_3$ is substituted with a $-Q_1$ group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

Preferably, in these more preferred compounds the Ar_3 cyclic group is selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$.

Preferred compounds of embodiments H, and J (forms 1 and 1) are those wherein:

R_3 is $-C(O)-CH_2-T_1-R_{11}$;

T_1 is O; and

R_{11} is $-C(O)-Ar_4$, wherein the Ar_4 cyclic group is selected from the set consisting of tetrazolyl, pyridyl, oxazolyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$.

Preferred compounds of embodiments H, I, and J employ formula (V), wherein R_3 is $-CO-CH_2-T_1-R_{11}$, R_{11} is $-Ar_4$, wherein the Ar_4 cyclic group is pyridyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$.

Preferred compounds of embodiment J (form 1) are those wherein:

R_3 is $-C(O)-H$, and

- 199 -

R₅ is -C(O)-R₁₀, wherein:

R₁₀ is Ar₃, wherein the Ar₃ cyclic group is phenyl optionally being singly or multiply substituted by:

-F,

5

-Cl,

-N(H)-R₅, wherein -R₅ is -H or -C(O)-R₁₀, wherein R₁₀ is a -C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein Ar₃ is phenyl,

10

-N(R₉)(R₁₀), wherein R₉ and R₁₀ are independently a -C₁₋₄ straight or branched alkyl group, or

-O-R₅, wherein R₅ is H or a -C₁₋₄ straight or branched alkyl group.

15 More preferably, Ar₃ is phenyl being optionally singly or multiply substituted at the 3- or 5-position by -Cl or at the 4-position by -NH-R₅, -N(R₉)(R₁₀), or -O-R₅.

Other more preferred compounds of embodiment J (form 1) are those wherein:

R₃ is -C(O)-H;

20

R₅ is -C(O)-R₁₀, wherein R₁₀ is Ar₃ and the Ar₃ cyclic group is selected from the group consisting of is indolyl, benzimidazolyl, thienyl, and benzo[b]thiophenyl, and said cyclic group optionally being singly or multiply substituted by -Q₁;

25

Other more preferred compounds of embodiment J (form 1) are those wherein:

R₃ is -C(O)-H;

R₅ is -C(O)-R₁₀, wherein R₁₀ is Ar₃ and the Ar₃

- 200 -

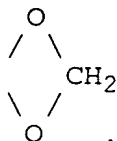
cyclic group is selected from quinolyl and isoquinolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$.

5 Other more preferred compounds of embodiment J (form 1) are those wherein:

R_3 is $-C(O)-H$;

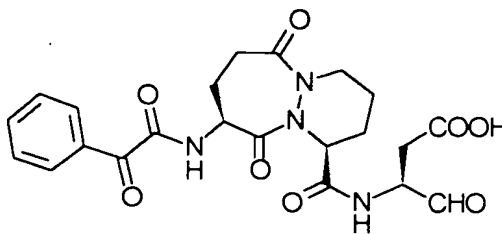
R_5 is $-C(O)-R_{10}$, wherein R_{10} is Ar_3 and the Ar_3 cyclic group is phenyl, substituted by

10

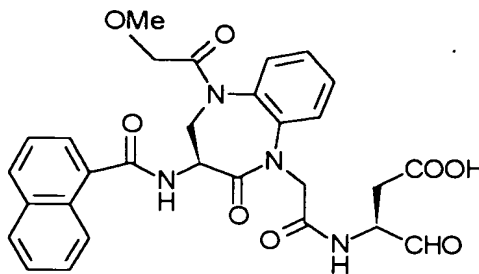


15 Preferred compounds of embodiment (J) include, but are not limited to:

2002

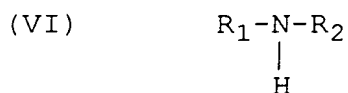


2201



- 201 -

The ICE inhibitors of another embodiment (K) of this invention are those of formula:

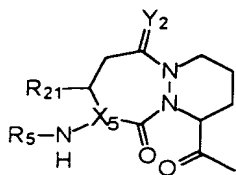


5

wherein:

R_1 is:

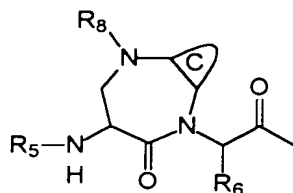
(e10)



, or

10

(w2)



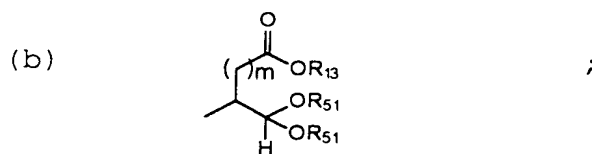
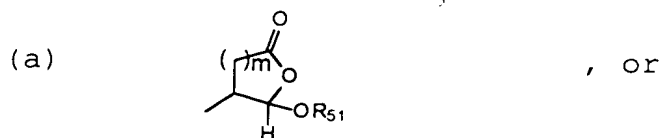
;

C is a ring chosen from the set consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl; the ring optionally being singly or multiply substituted by $-Q_1$;

15

R_2 is:

- 202 -



m is 1 or 2;

5 each R₅ is independently selected from the group consisting of:

- C(O)-R₁₀,
- C(O)O-R₉,
- C(O)-N(R₁₀)(R₁₀)
- 10 -S(O)₂-R₉,
- S(O)₂-NH-R₁₀,
- C(O)-CH₂-O-R₉,
- C(O)C(O)-R₁₀,
- R₉,
- 15 -H,
- C(O)C(O)-OR₁₀, and
- C(O)C(O)-N(R₉)(R₁₀);

X₅ is CH or N;

20 Y₂ is H₂ or O;

R₆ is selected from the group consisting of -H and -CH₃;

25 R₈ is selected from the group consisting of:

- 203 -

-C(O)-R₁₀,
 -C(O)O-R₉,
 -C(O)-N(H)-R₁₀,
 -S(O)₂-R₉,
 5 -S(O)₂-NH-R₁₀,
 -C(O)-CH₂-OR₁₀,
 -C(O)C(O)-R₁₀;
 -C(O)-CH₂N(R₁₀)(R₁₀),
 -C(O)-CH₂C(O)-O-R₉,
 10 -C(O)-CH₂C(O)-R₉,
 -H, and
 -C(O)-C(O)-OR₁₀;

each R₉ is independently selected from the group
 consisting of -Ar₃ and a -C₁₋₆ straight or branched
 15 alkyl group optionally substituted with Ar₃, wherein
 the -C₁₋₆ alkyl group is optionally unsaturated;

each R₁₀ is independently selected from the group
 consisting of -H, -Ar₃, a -C₃₋₆ cycloalkyl group, and a
 -C₁₋₆ straight or branched alkyl group optionally
 20 substituted with Ar₃, wherein the -C₁₋₆ alkyl group is
 optionally unsaturated;

R₁₃ is selected from the group consisting of H,
 Ar₃, and a -C₁₋₆ straight or branched alkyl group
 optionally substituted with Ar₃, -CONH₂, -OR₅, -OH,
 25 -OR₉, or -CO₂H;

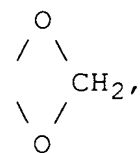
each R₅₁ is independently selected from the group
 consisting of R₉, -C(O)-R₉, -C(O)-N(H)-R₉, or each R₅₁
 taken together forms a saturated 4-8 member carbocyclic
 ring or heterocyclic ring containing -O-, -S-, or -NH-;

- 204 -

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

5 each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2 , =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5 , $-OR_5$, $-NHR_5$, $-OR_9$, $-N(R_9)(R_{10})$, $-R_9$, $-C(O)-R_{10}$, and



25 provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

30 Preferred compounds of this embodiment are those wherein:

m is 1;

- 205 -

C is a ring chosen from the set consisting of benzo, pyrido, or thieno the ring optionally being singly or multiply substituted by halogen, -NH₂, -NH-R₅, -NH-R₉, -OR₁₀, or -R₉, wherein R₉ is a straight or branched C₁₋₄ alkyl group and R₁₀ is H or a straight or branched C₁₋₄ alkyl group;

R₆ is H;

R₁₃ is H or a C₁₋₄ straight or branched alkyl group optionally substituted with Ar₃, -OH, -OR₉, -CO₂H, wherein the R₉ is a C₁₋₄ branched or straight chain alkyl group; wherein Ar₃ is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q₁;

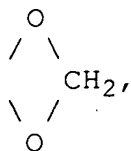
R₂₁ is -H or -CH₃;

R₅₁ is a C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein Ar₃ is phenyl, optionally substituted by -Q₁;

each Ar₃ cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by -Q₁;

each Q₁ is independently selected from the group consisting of -NH₂, -Cl, -F, -Br, -OH, -R₉, -NH-R₅ wherein R₅ is -C(O)-R₁₀ or -S(O)₂-R₉, -OR₅ wherein R₅ is -C(O)-R₁₀, -OR₉, -NHR₉, and

- 206 -



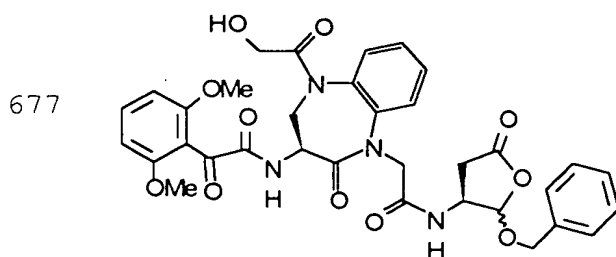
5

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 wherein Ar_3 is phenyl;

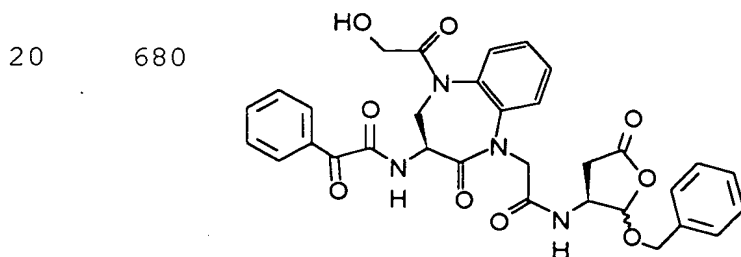
10 provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

15 Preferably, in this preferred embodiment, R_1 is (w2) and the other substituents are as defined above.

Compounds of this preferred embodiment include, but are not limited to:



; and



More preferably, R_8 is selected from the

- 207 -

group consisting of:

-C(O)-R₁₀,
-C(O)O-R₉,
-C(O)-CH₂-OR₁₀, and
5 -C(O)-CH₂C(O)-R₉.

Most preferably, R₈ is -C(O)-CH₂-OR₁₀ and R₁₀ is -H or -CH₃.

Alternatively, in this preferred embodiment, R₁ is (e10) and X₅ is CH and the other substituents are
10 as defined above.

Alternatively, in this preferred embodiment, R₁ is (e10) and X₅ is N and the other substituents are as defined above.

Preferably, in any of the above compounds of
15 embodiment (K), R₅ is -C(O)-R₁₀ or -C(O)-C(O)-R₁₀ and the other substituents are as defined above.

More preferably, R₁₀ is -Ar₃ and the other substituents are as defined above.

More preferably, in these more preferred
20 compounds:

R₅ is -C(O)-R₁₀ and R₁₀ is Ar₃,

wherein the Ar₃ cyclic group is phenyl optionally being singly or multiply substituted by:

-R₉, wherein R₉ is a C₁₋₄ straight or branched
25 alkyl group;

-F,

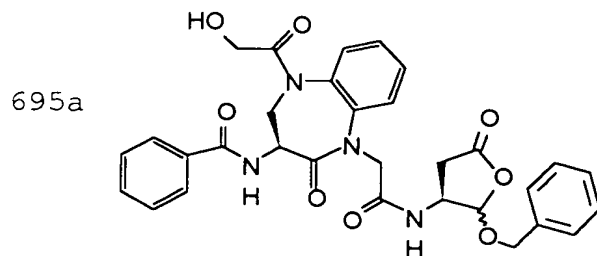
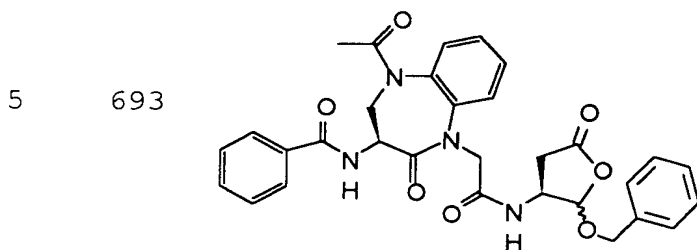
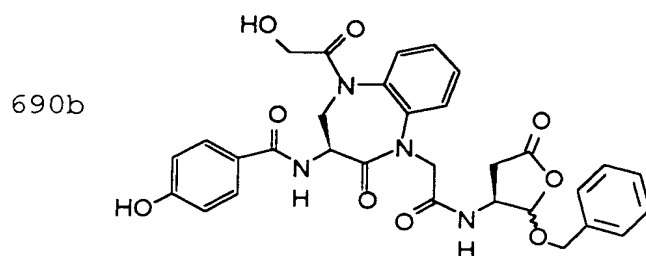
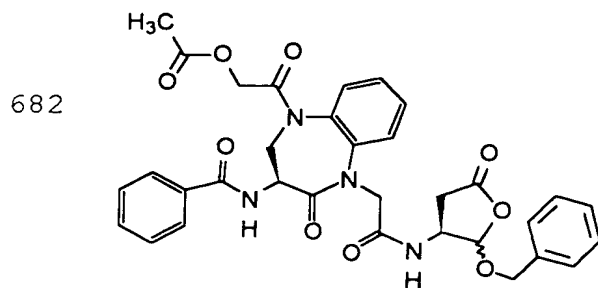
-Cl,

-N(H)-R₅, wherein -R₅ is -H or -C(O)-R₁₀, wherein R₁₀ is a -C₁₋₆ straight or branched alkyl group
30 optionally substituted with Ar₃, wherein Ar₃ is phenyl,
-N(R₉)(R₁₀), wherein R₉ and R₁₀ are independently a -C₁₋₄ straight or branched alkyl group, or

-O-R₅, wherein R₅ is H or a -C₁₋₄ straight or branched alkyl group.

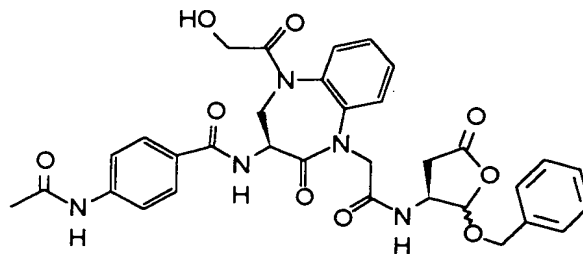
- 208 -

Preferred compounds of this more preferred embodiment include, but are not limited to:



- 209 -

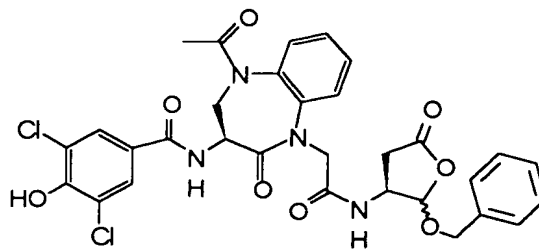
695b



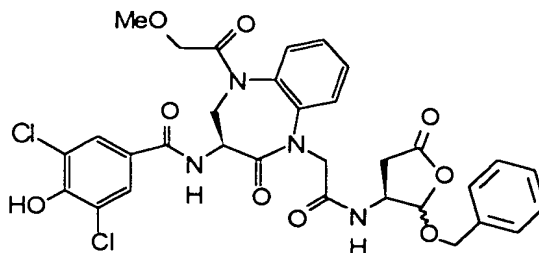
Most preferably, Ar_3 is phenyl being singly or multiply substituted at the 3- or 5-position by -Cl or at the 4-position by -NH- R_5 ,
 5 -N(R_9) (R_{10}), or -O- R_5 .

Preferred compounds of this most preferred embodiment include, but are not limited to:

655



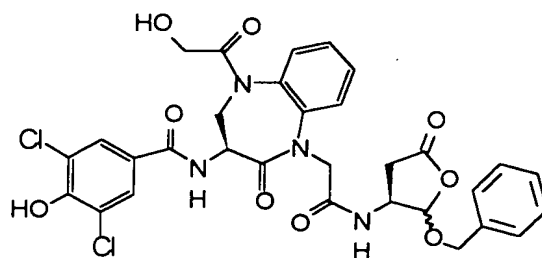
688a



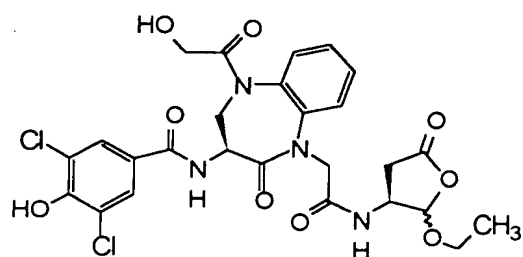
10

- 210 -

692a

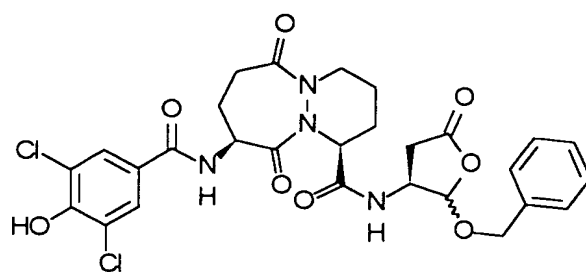


692b

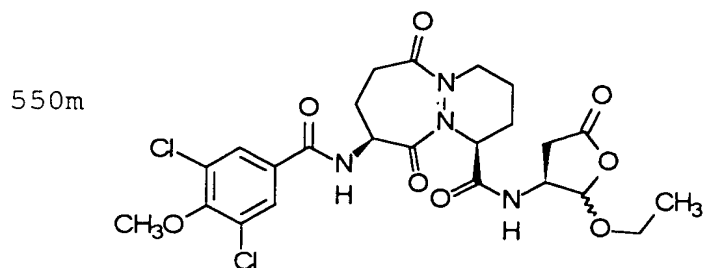
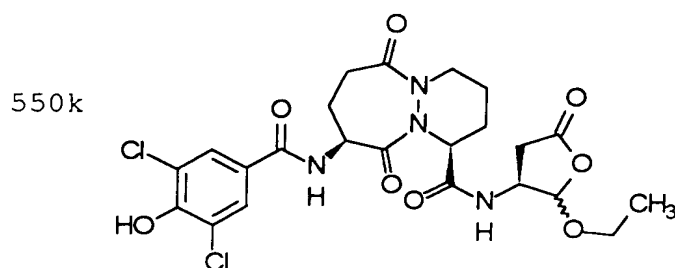
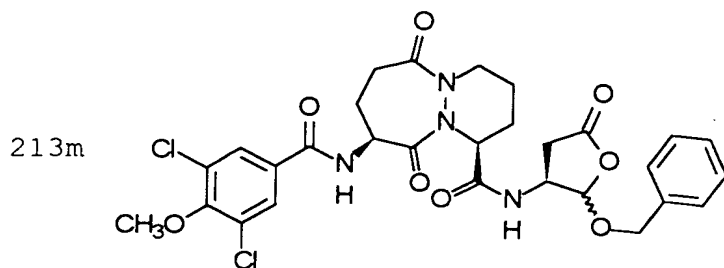


Other preferred compounds of
this most preferred embodiment include, but are not
limited to:

213k



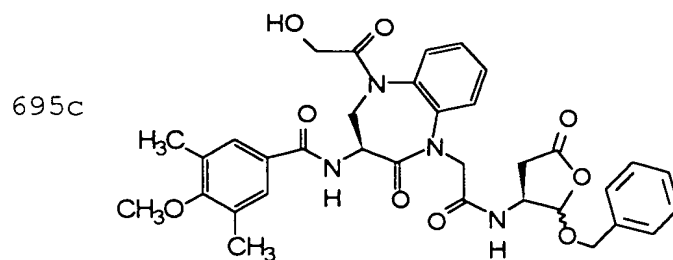
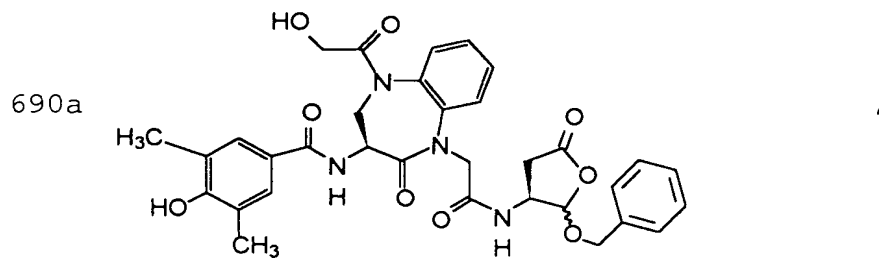
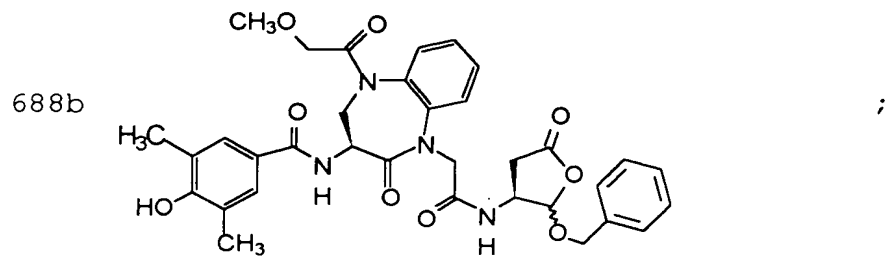
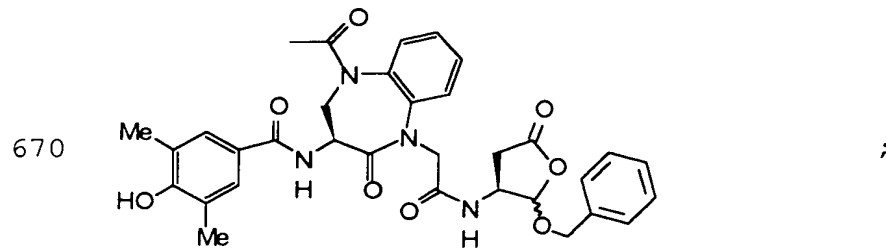
- 211 -



Alternatively, Ar₃ is phenyl being
 5 singly or multiply substituted at the 3- or 5-position
 by -R₉, wherein R₉ is a C₁₋₄ straight or branched alkyl
 group; and at the 4-position by -O-R₅.

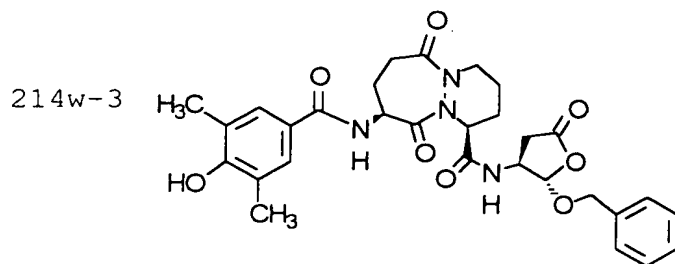
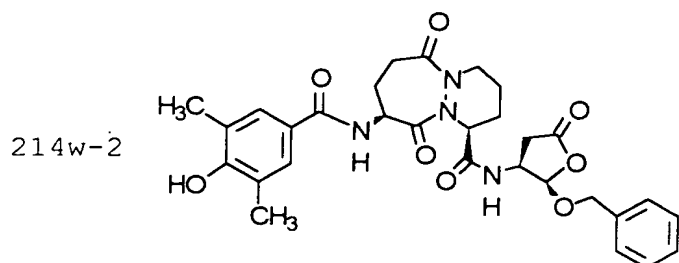
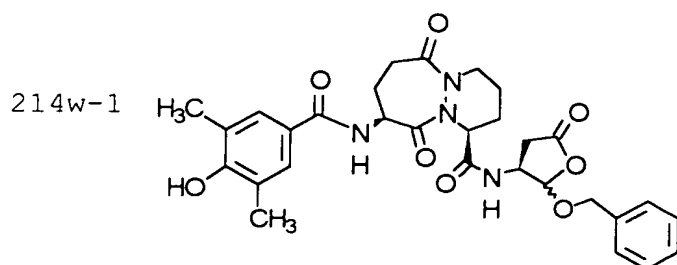
Preferred compounds of this
 most preferred embodiment include, but are not limited
 10 to:

- 212 -



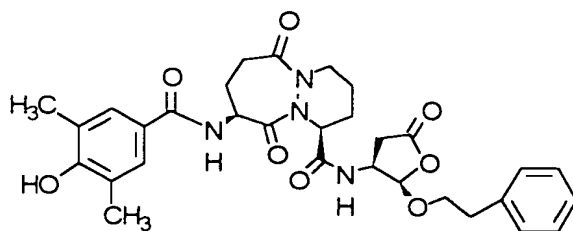
- 213 -

limited to:

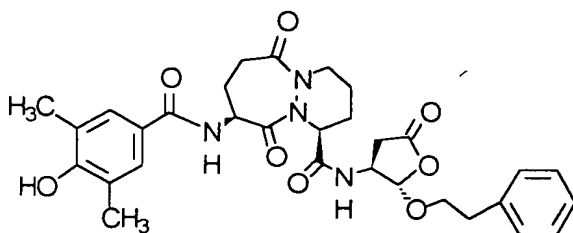


5

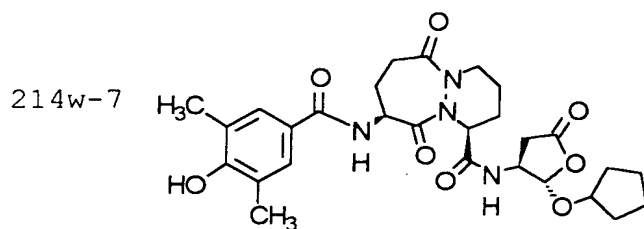
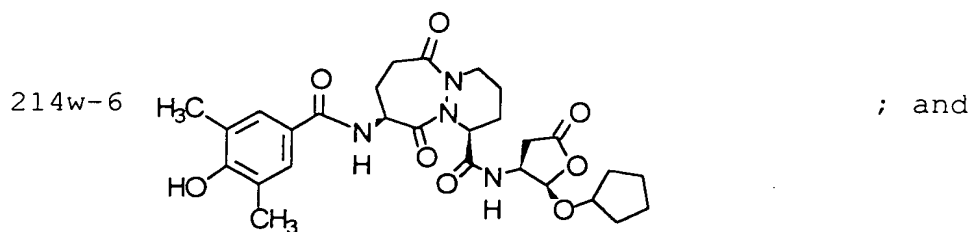
214w-4



214w-5



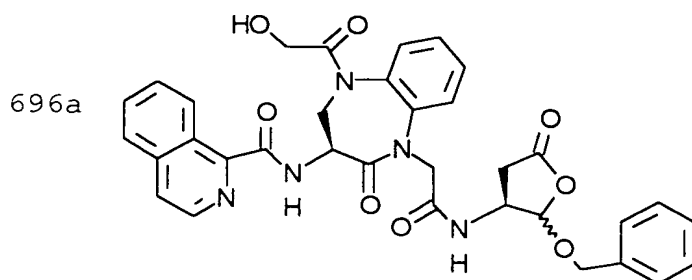
- 214 -



Alternatively, in this more preferred embodiment, R_5 is $-C(O)-R_{10}$, wherein R_{10} is Ar_3 and the Ar_3 cyclic group is selected from the group consisting of is indolyl, benzimidazolyl, thienyl, quinolyl, isoquinolyl and benzo[b]thiophenyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$.

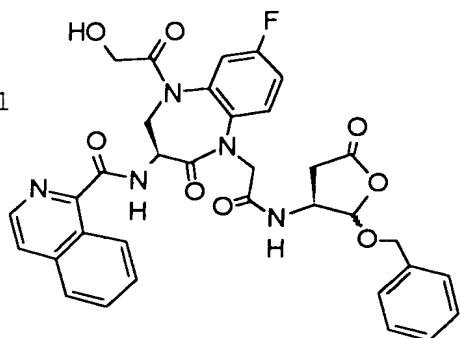
Most preferably, the Ar_3 cyclic group is isoquinolyl.

Preferred compounds of this most preferred embodiment include, but are not limited to:

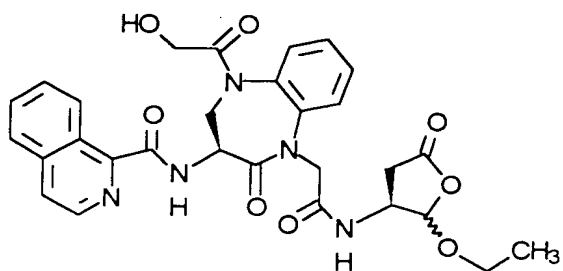


- 215 -

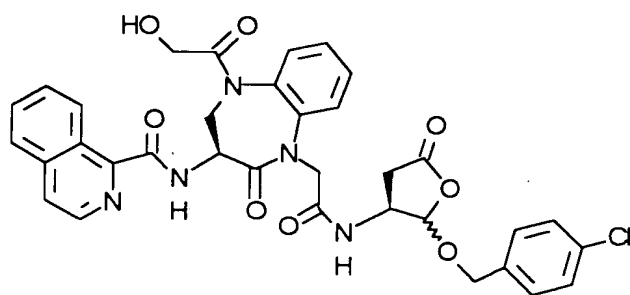
696a-1



696b

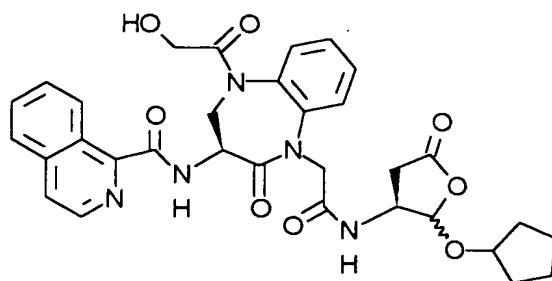


696c

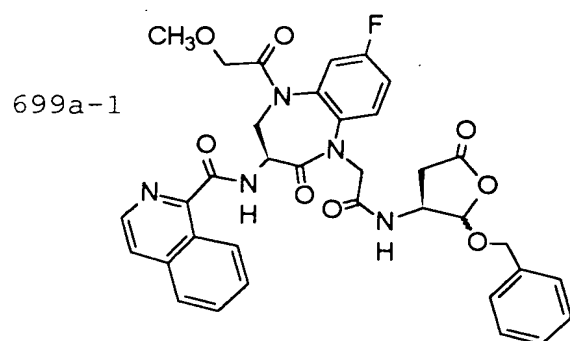
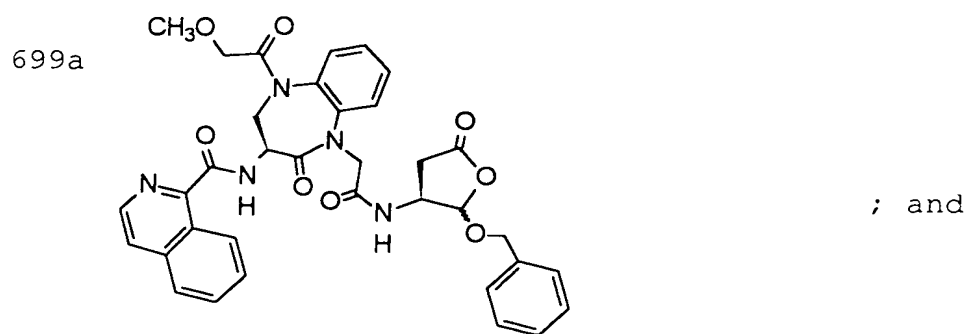
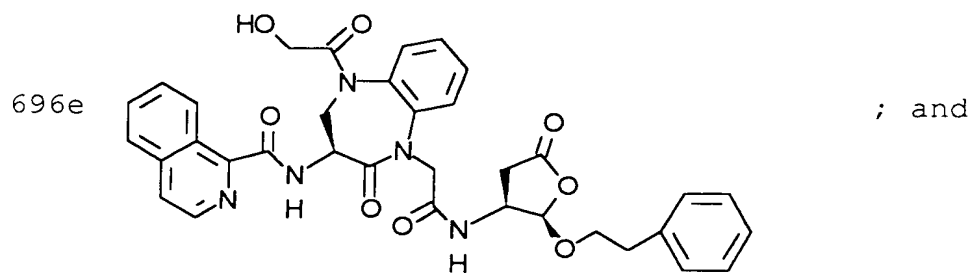


5

696d



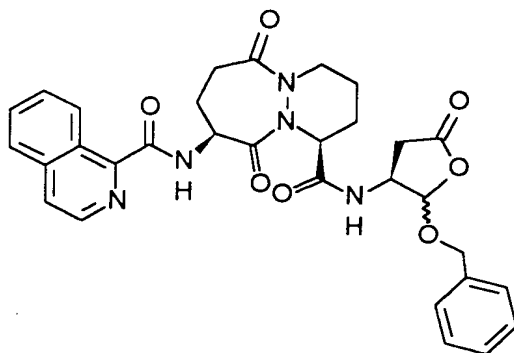
- 216 -



Other preferred compounds of this most preferred embodiment include, but are not limited to:

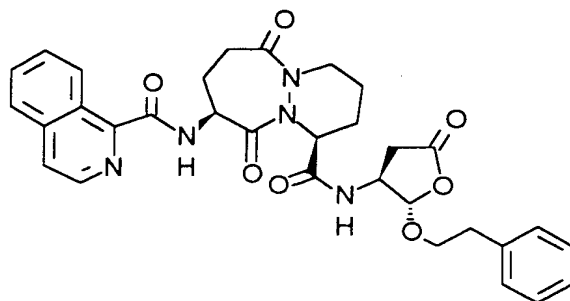
- 217 -

213y



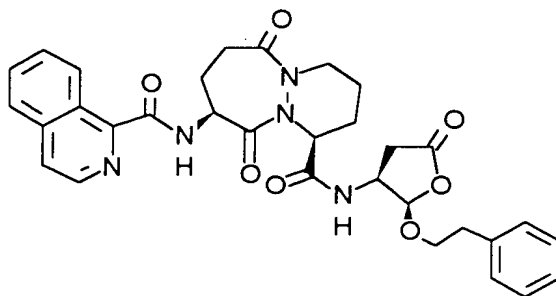
;

412a



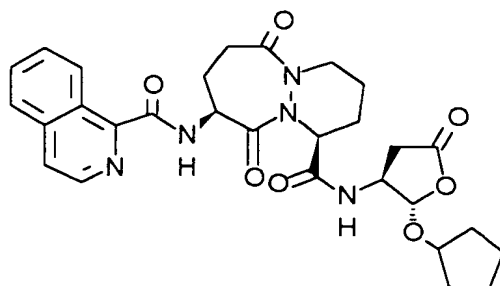
;

412b



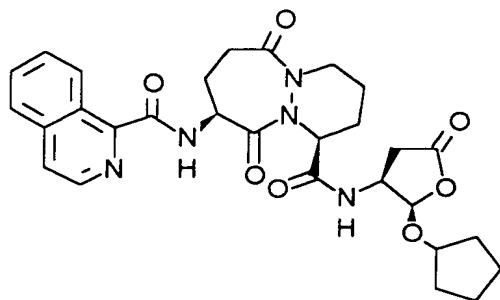
;

412c



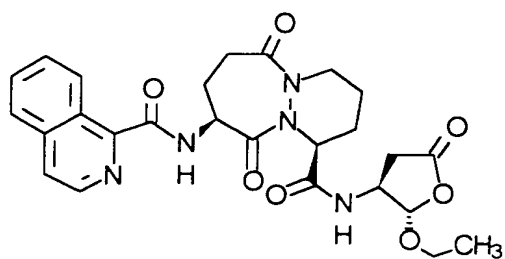
;

412d

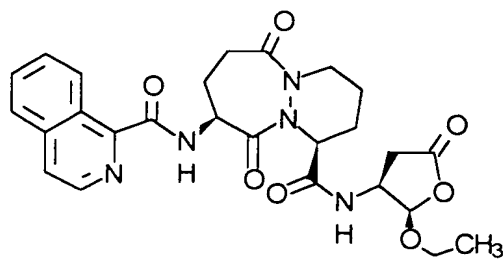


;

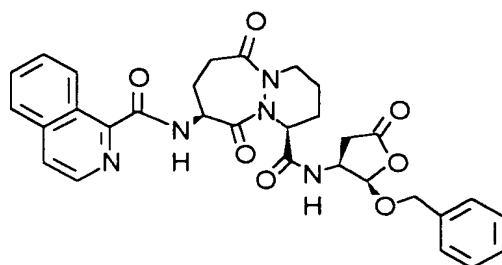
412e

*i*

412f

*i*

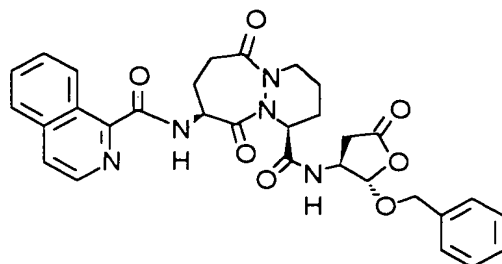
412g



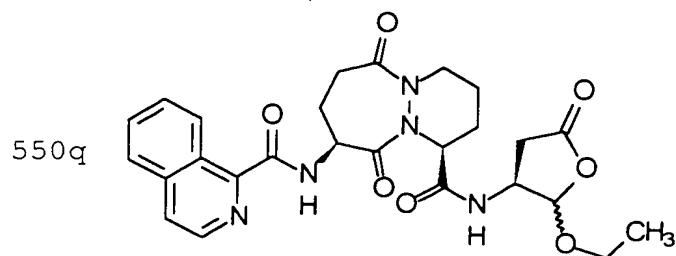
i

5

412h

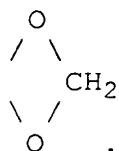
*i*

- 219 -



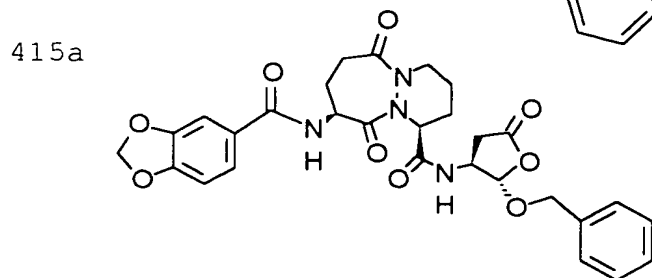
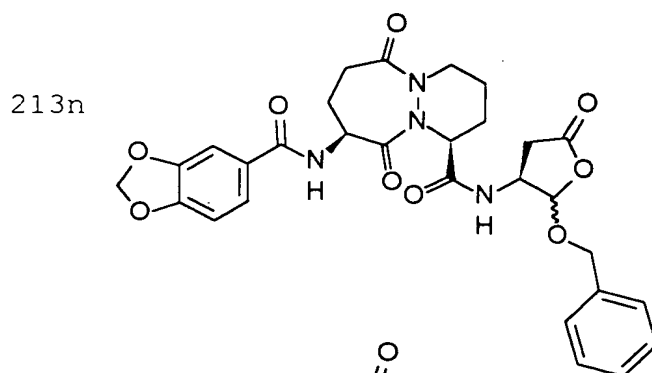
Alternatively, in this more preferred embodiment, R_5 is $-C(O)-R_{10}$, wherein R_{10} is Ar_3 and the Ar_3 cyclic group is phenyl, substituted by

5



10

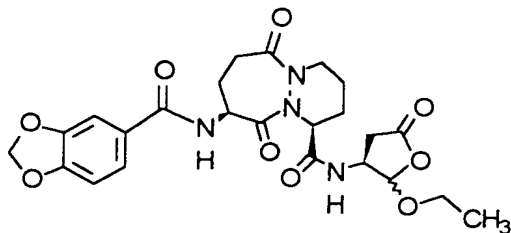
Preferred compounds of this more preferred embodiment include, but are not limited to:



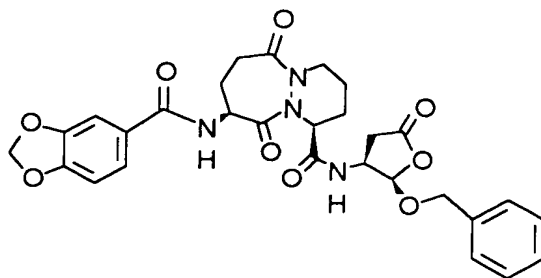
- 220 -

415b

; and

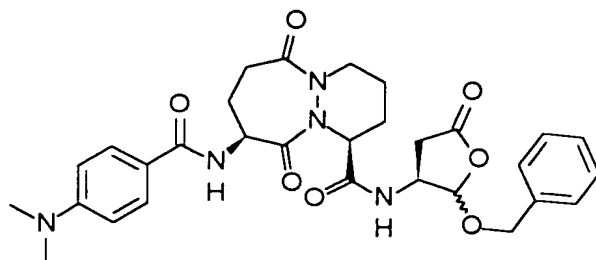


415c

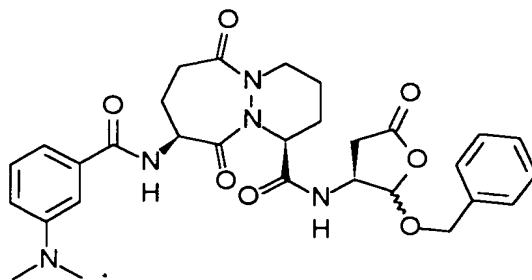


Other compounds of embodiment (K) include,
5 but are not limited to:

213f

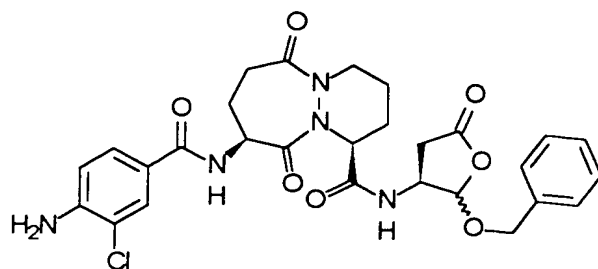


213g



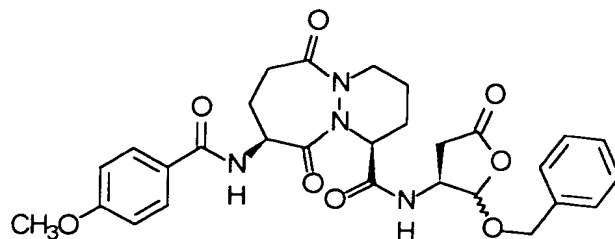
- 221 -

213h



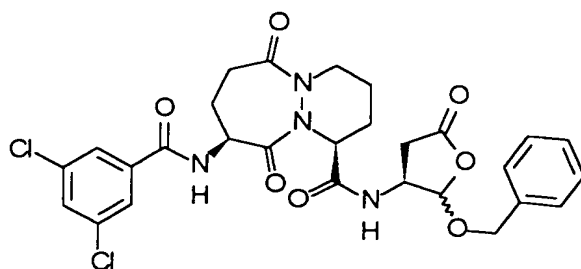
;

213i



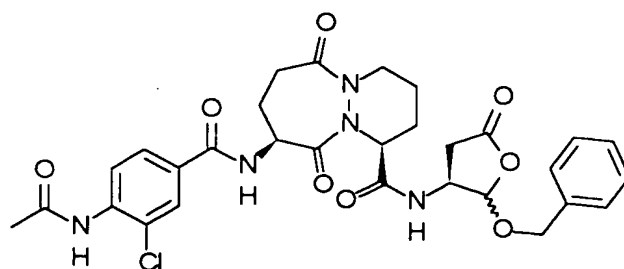
;

213j



;

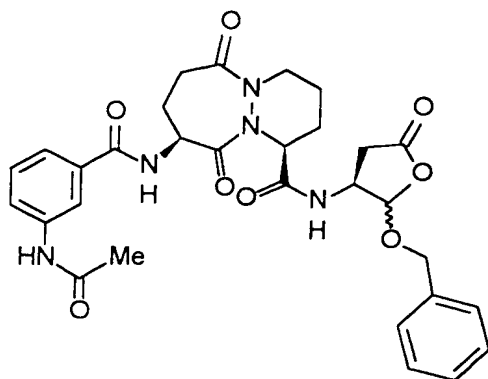
213l



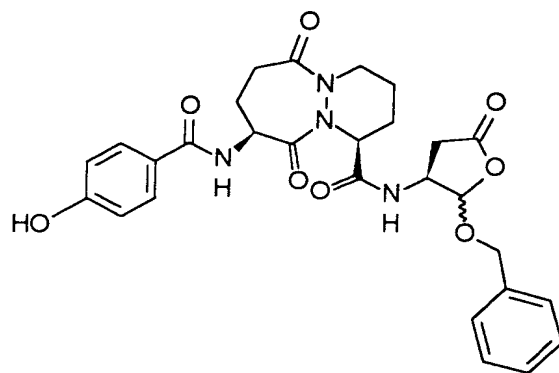
;

- 222 -

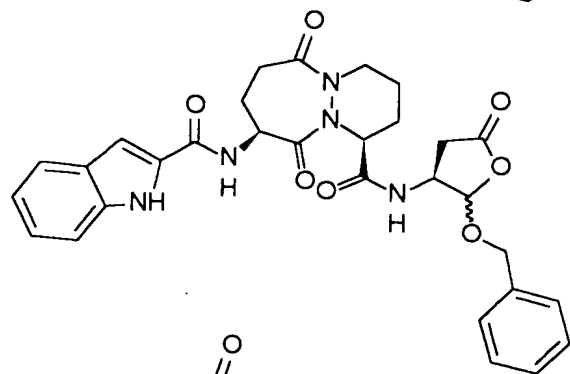
213o



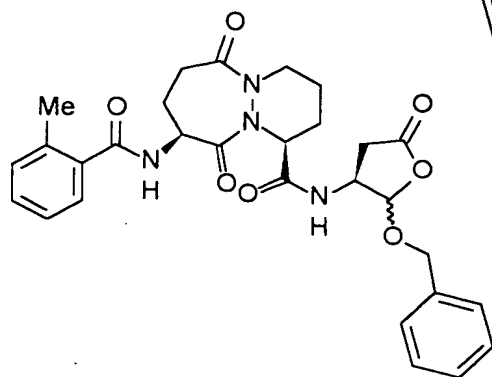
213p



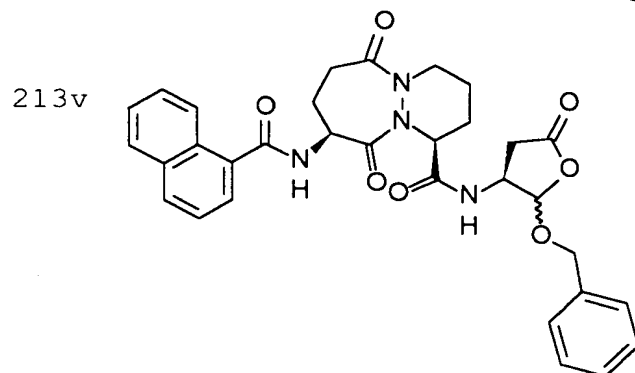
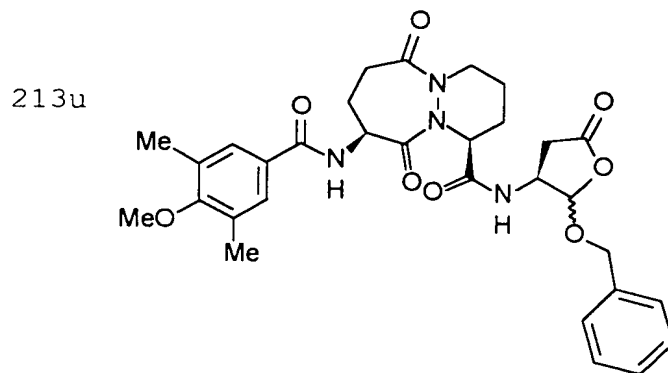
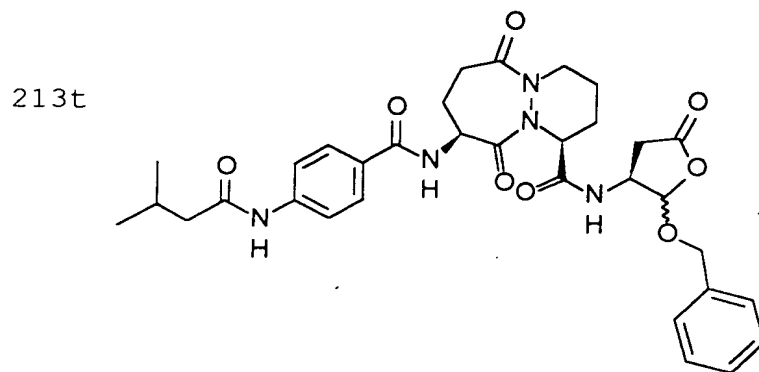
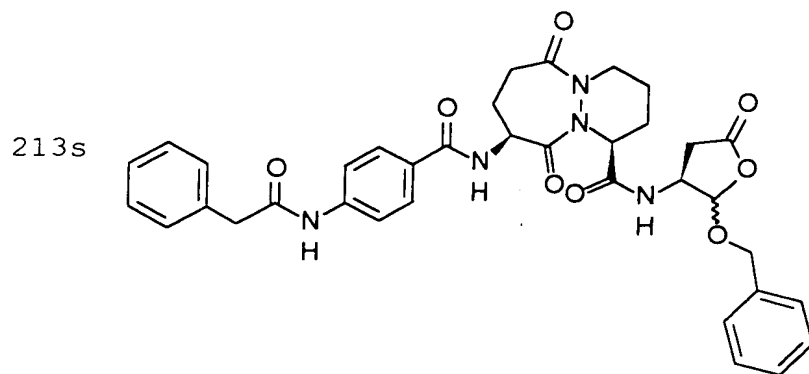
213q



213r

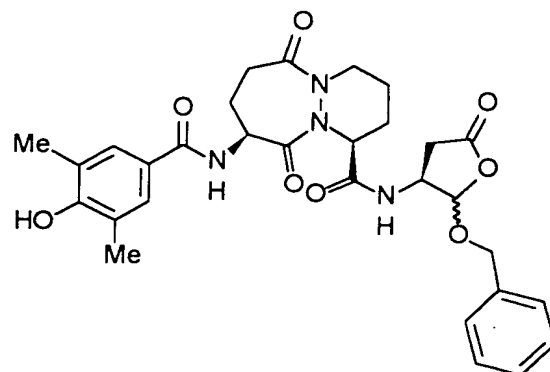


- 223 -

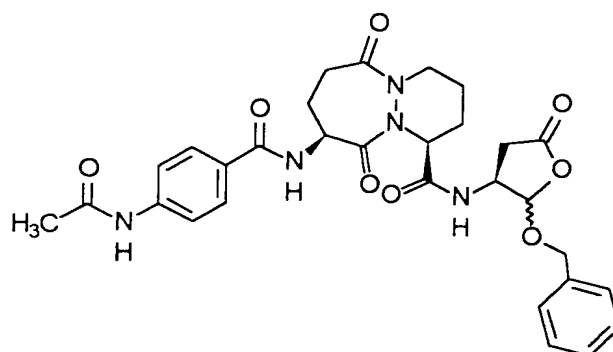


- 224 -

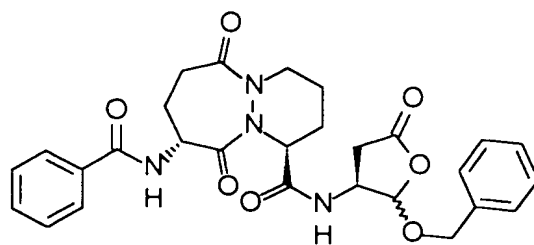
213w



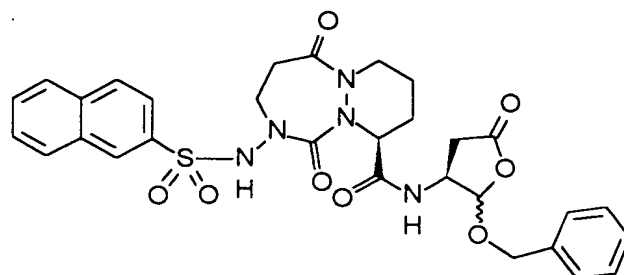
213x



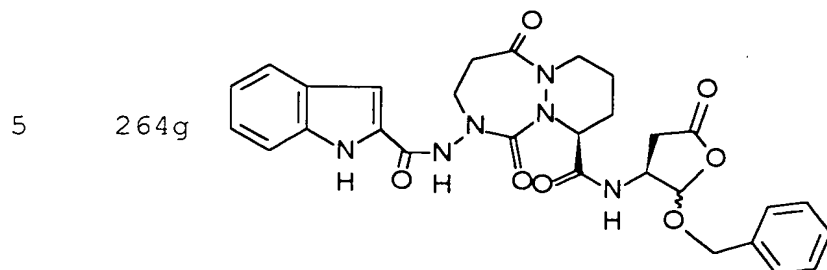
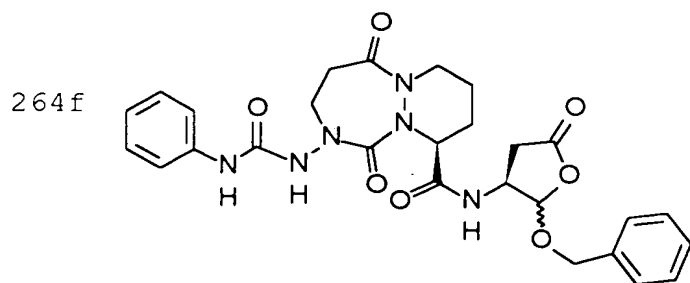
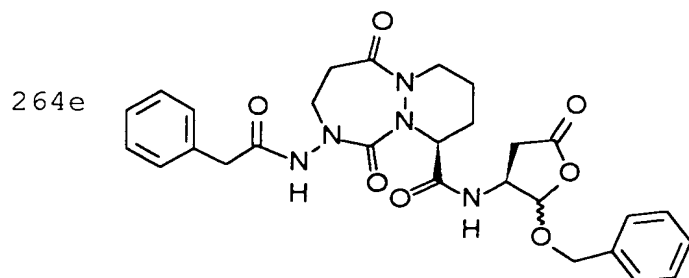
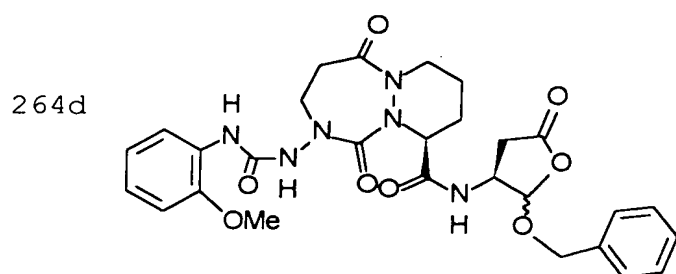
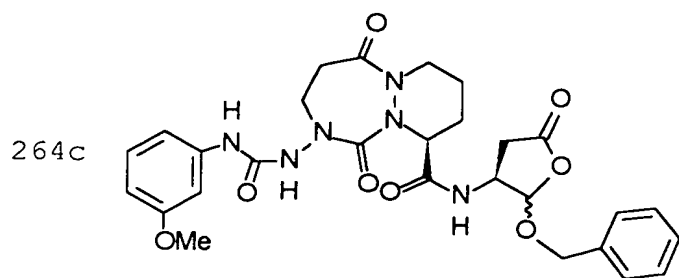
245b



264a

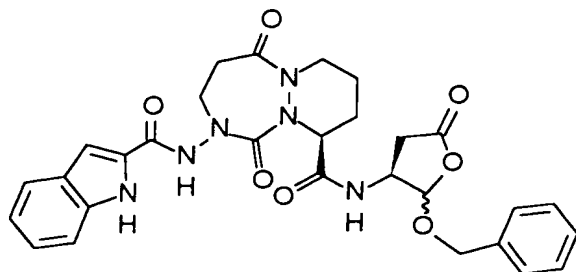


- 225 -

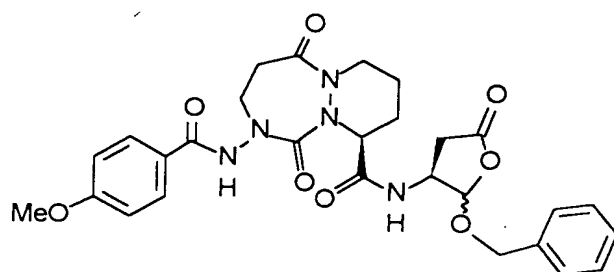


- 226 -

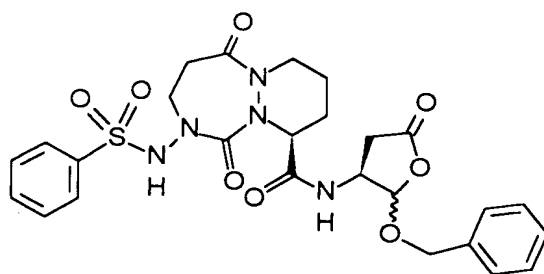
264h



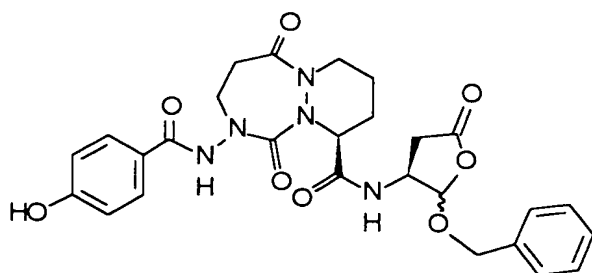
264i



264j

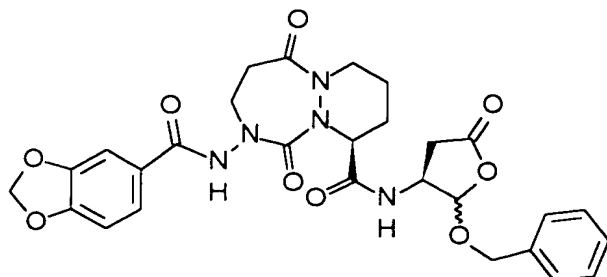


264k



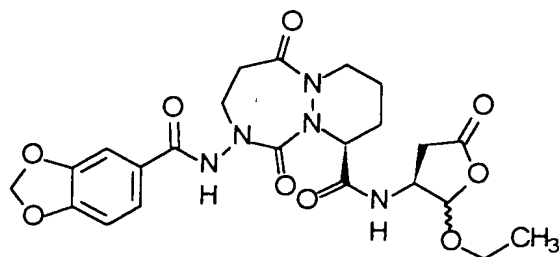
5

264l

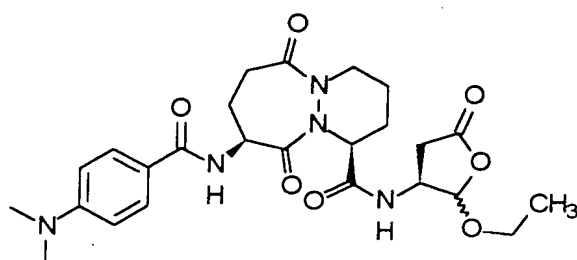


- 227 -

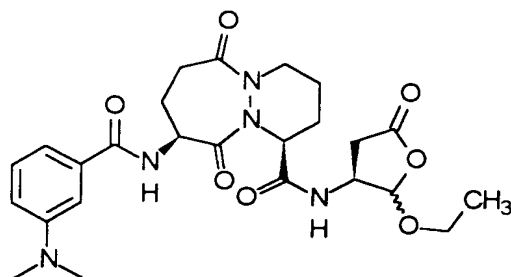
528



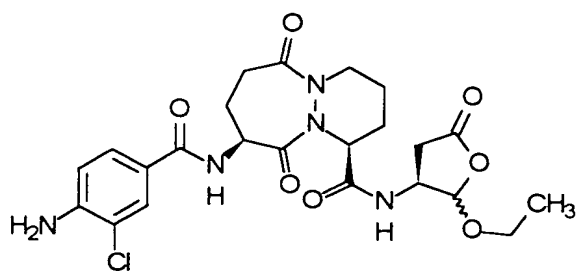
550f



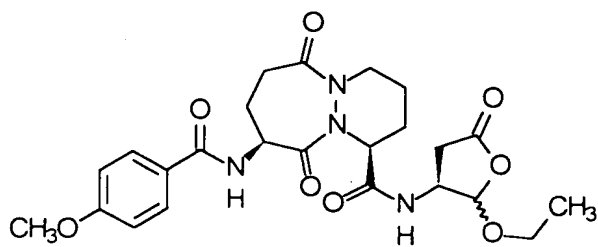
550g



550h

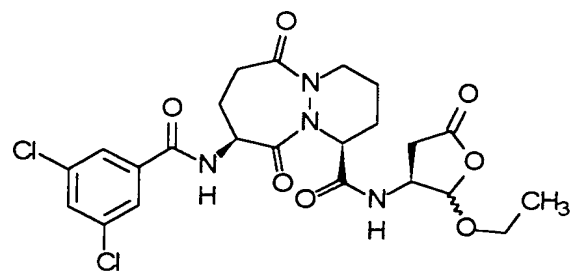


5 550i



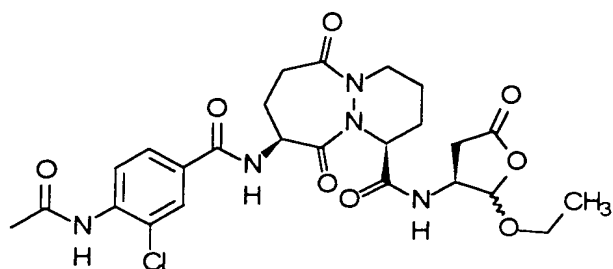
- 228 -

550j



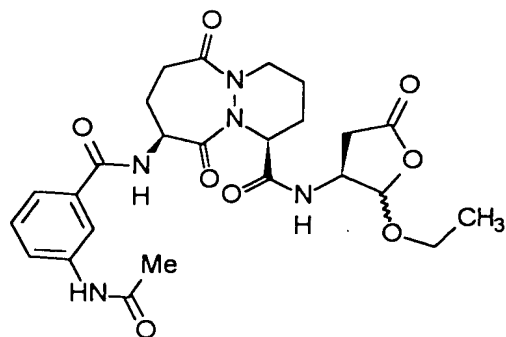
;

550l



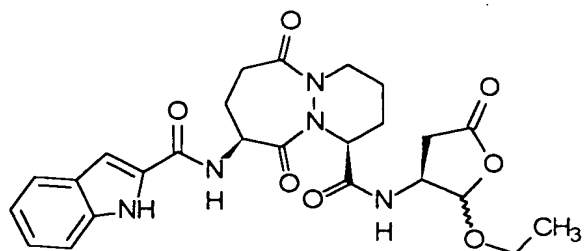
;

550n



;

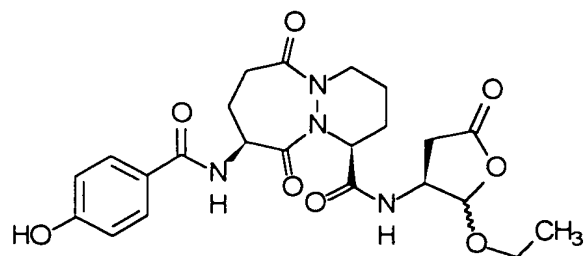
550o



;

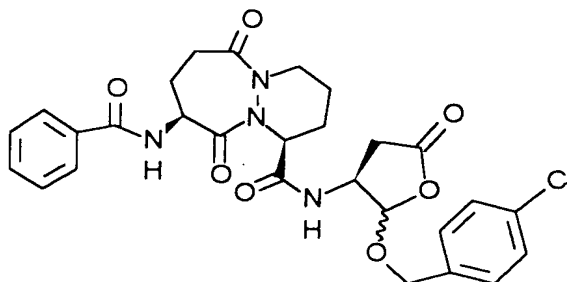
5

550p

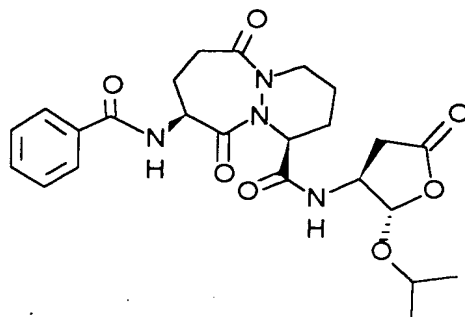


;

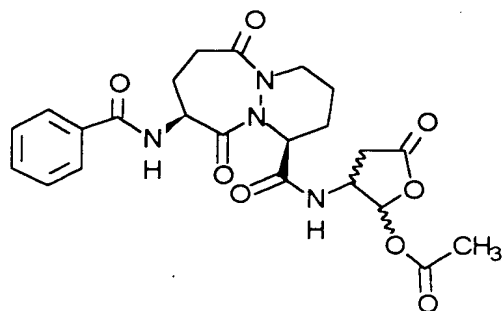
2100f



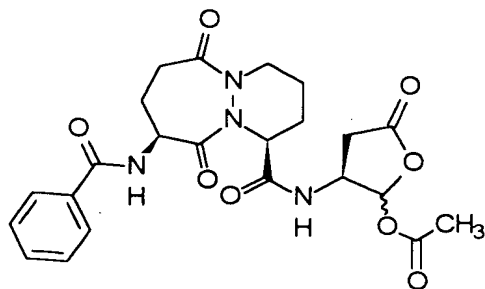
2100g



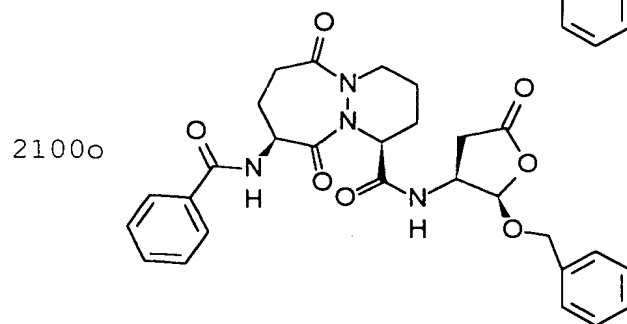
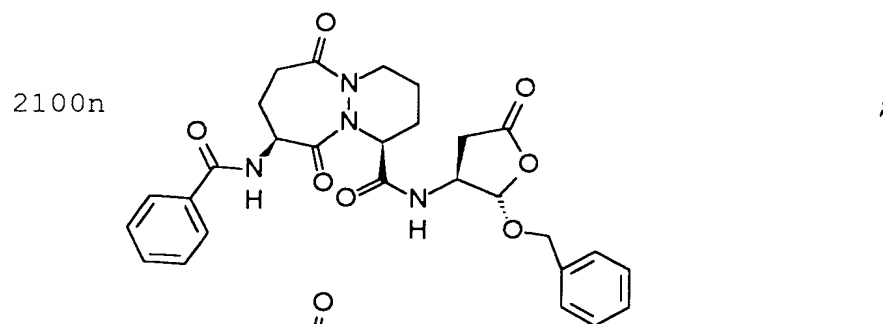
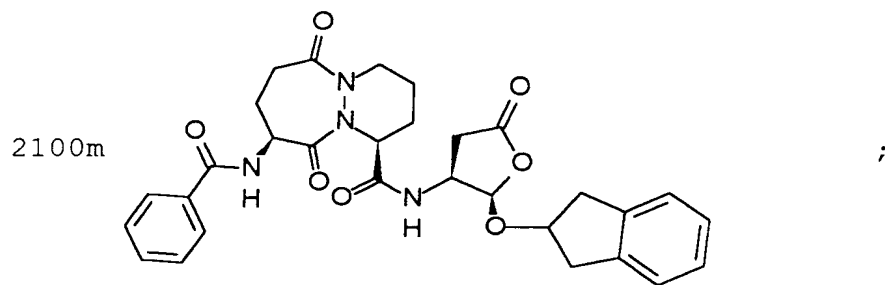
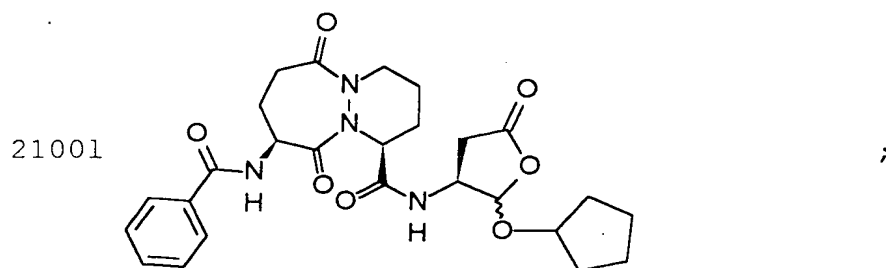
2100h



2100k

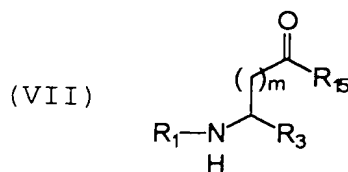


- 230 -



5 The ICE inhibitors of another embodiment (L)
of this invention are those of formula :

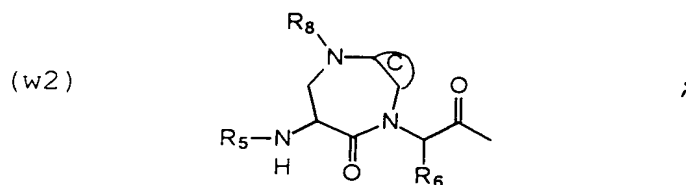
- 231 -



wherein:

m is 1 or 2;

- 5 R₁ is selected from the group consisting of the following formulae:



- 10 C is a ring chosen from the set consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl, the ring optionally being singly or multiply substituted by -Q₁;

- 15 R₃ is selected from the group consisting of:

-CN,
 -C(O)-H,
 -C(O)-CH₂-T₁-R₁₁,
 -C(O)-CH₂-F,
 20 -C=N-O-R₉, and
 -CO-Ar₂;

each R₅ is independently selected from the group consisting of:

- 25 -C(O)-R₁₀,
 -C(O)O-R₉,

- 232 -

-C(O)-N(R₁₀)(R₁₀)
 -S(O)₂-R₉,
 -S(O)₂-NH-R₁₀,
 -C(O)-CH₂-O-R₉,
 5 -C(O)C(O)-R₁₀,
 -R₉,
 -H,
 -C(O)C(O)-OR₁₀, and
 -C(O)C(O)-N(R₉)(R₁₀);

10

each T₁ is independently selected from the group consisting of -O-, -S-, -S(O)-, and -S(O)₂-;

15 R₆ is selected from the group consisting of -H and
 -CH₃;

R₈ is selected from the group consisting of:

-C(O)-R₁₀,
 -C(O)O-R₉,
 -C(O)-NH-R₁₀,
 20 -S(O)₂-R₉,
 -S(O)₂-NH-R₁₀,
 -C(O)-CH₂-OR₁₀,
 -C(O)C(O)-R₁₀,
 -C(O)-CH₂-N(R₁₀)(R₁₀),
 25 -C(O)-CH₂C(O)-O-R₉,
 -C(O)-CH₂C(O)-R₉,
 -H, and
 -C(O)-C(O)-OR₁₀;

30 each R₉ is independently selected from the group
 consisting of -Ar₃ and a -C₁₋₆ straight or branched
 alkyl group optionally substituted with Ar₃, wherein
 the -C₁₋₆ alkyl group is optionally unsaturated;

- 233 -

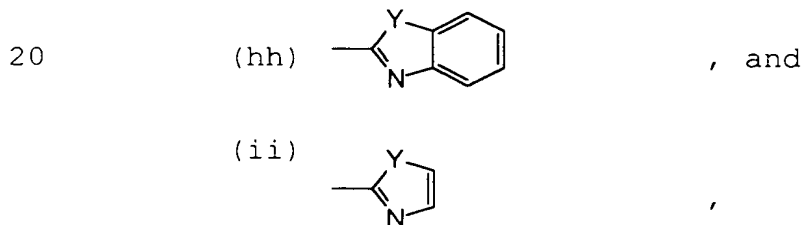
each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a C_{3-6} cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 , wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{11} is independently selected from the group consisting of:

- Ar_4 ,
 $-(CH_2)_{1-3}-Ar_4$,
 -H, and
 $-C(O)-Ar_4$;

R_{15} is selected from the group consisting of -OH, $-OAr_3$, $-N(H)-OH$, and $-OC_{1-6}$, wherein C_{1-6} is a straight or branched alkyl group optionally substituted with Ar_3 , $-CONH_2$, $-OR_5$, $-OH$, $-OR_9$, or $-CO_2H$;

Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by $-Q_1$ or phenyl, optionally substituted by Q_1 :



wherein each Y is independently selected from the group consisting of O and S;

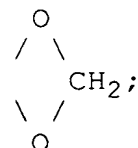
each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains

- 234 -

6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO₂, =N-, and -NH-,
 5 -N(R₅)-, and -N(R₉)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or
 10 multiply substituted by -Q₁;

each Ar₄ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and
 15 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO₂, =N-, -NH-, -N(R₅)-, and -N(R₉)- said heterocycle group optionally containing one or more double bonds, said heterocycle
 20 group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q₁;

each Q₁ is independently selected from the group consisting of -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH, -perfluoro C₁₋₃ alkyl, R₅, -OR₅, -NHR₅, -OR₉,
 25 -N(R₉)(R₁₀), -R₉, -C(O)-R₁₀, and



30

provided that when -Ar₃ is substituted with a Q₁ group which comprises one or more additional -Ar₃

- 235 -

groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

Preferably,

m is 1;

5 C is a ring chosen from the set consisting of benzo, pyrido, and thieno, the ring optionally being singly or multiply substituted by halogen, $-NH_2$, $-NH-R_5$, or $-NH-R_9$, $-OR_{10}$, or $-R_9$, wherein R_9 is a straight or branched $-C_{1-4}$ alkyl group, and R_{10} is $-H$ or
10 a straight or branched $-C_{1-4}$ alkyl group;

T_1 is O or S;

R_6 is H;

15 R_{11} is selected from the group consisting of $-Ar_4$, $-(CH_2)_{1-3}-Ar_4$, and $-C(O)-Ar_4$;

Ar_2 is (hh);

Y is O;

20 each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply
25 substituted by $-Q_1$;

 each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl,

- 236 -

naphthyl, pyridinyl, oxazolyl, pyrimidinyl, or indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

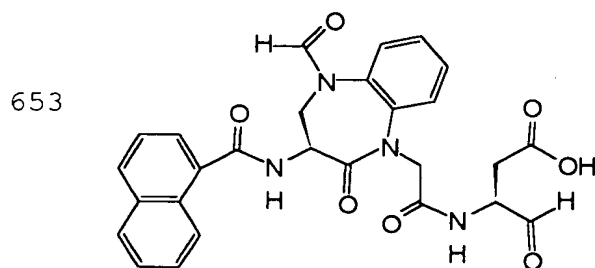
each Q_1 is independently selected from the group consisting of $-NH_2$, $-Cl$, $-F$, $-Br$, $-OH$, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and



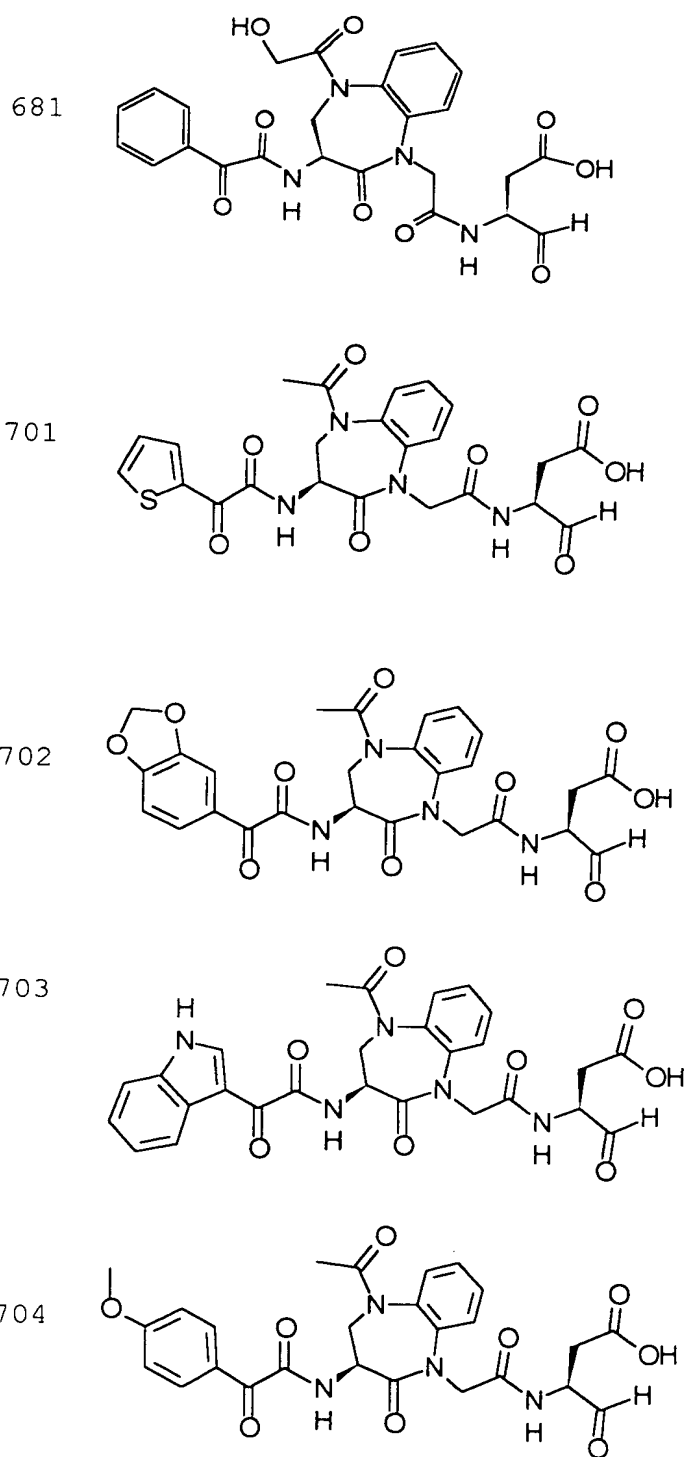
wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

Preferred compounds of this preferred embodiment include, but are not limited to:

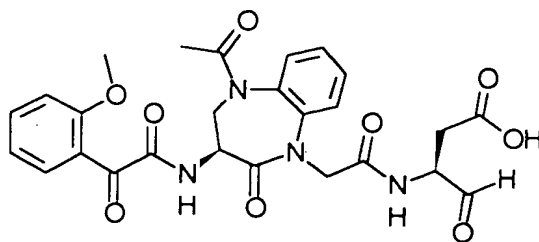


- 237 -



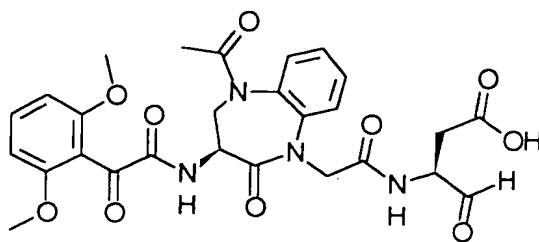
- 238 -

705



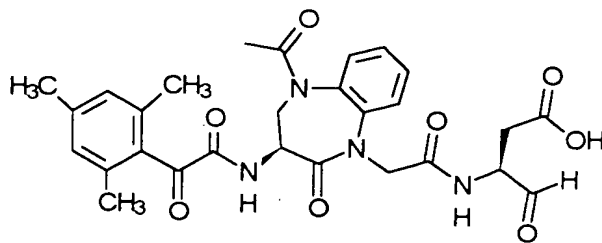
;

706



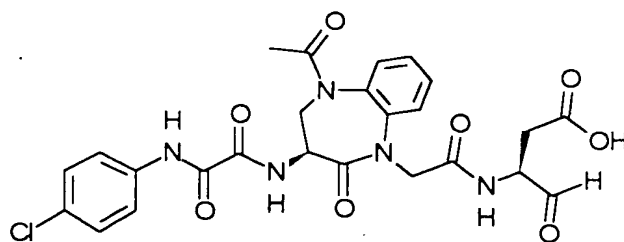
;

709



;

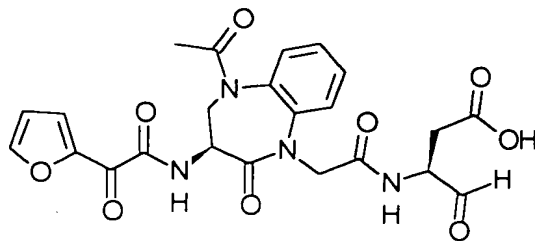
710



;

5

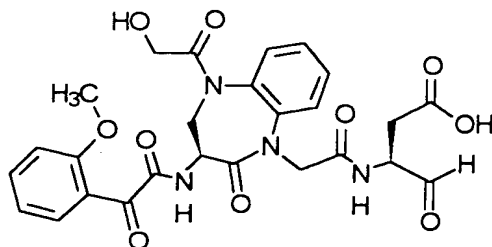
711



; and

- 239 -

921



More preferably, R_3 is $-C(O)-Ar_2$ and the other substituents are as described above.

Alternatively, R_3 is

5 $-C(O)CH_2-T_1-R_{11}$;

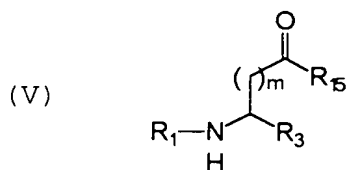
Alternatively, R_3 is $-C(O)-H$.

Preferably, in any of the above compounds of embodiment (L), R_8 is selected from the group consisting of:

10 $-C(O)-R_{10}$,
 $-C(O)O-R_9$,
 $-C(O)-CH_2-OR_{10}$, and
 $-C(O)-CH_2C(O)-R_9$.

15 More preferably, R_8 is $-C(O)-CH_2-OR_{10}$ and R_{10} is $-H$ or $-CH_3$.

Alternatively, ICE inhibitors of embodiment (L) of this invention are those of formula :



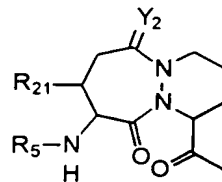
wherein:

20 m is 1;

R_1 is:

- 240 -

(e10-B)



;

R_3 is selected from the group consisting of:

- CN,
- C(O)-H,
- C(O)-CH₂-T₁-R₁₁,
- C(O)-CH₂-F,
- C=N-O-R₉, and
- CO-Ar₂;

each R_5 is independently selected from the group consisting of:

- C(O)-R₁₀,
- C(O)O-R₉,
- C(O)-N(R₁₀)(R₁₀)
- S(O)₂-R₉,
- S(O)₂-NH-R₁₀,
- C(O)-CH₂-O-R₉,
- C(O)C(O)-R₁₀,
- R₉,
- H,
- C(O)C(O)-OR₁₀, and
- C(O)C(O)-N(R₉)(R₁₀);

Y_2 is H₂ or O;

each T₁ is independently selected from the group consisting of -O- or -S-;

each R₉ is independently selected from the group

- 241 -

consisting of $-\text{Ar}_3$ and a $-\text{C}_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 , wherein the $-\text{C}_{1-6}$ alkyl group is optionally unsaturated;

5 each R_{10} is independently selected from the group consisting of $-\text{H}$, $-\text{Ar}_3$, a C_{3-6} cycloalkyl group, and a $-\text{C}_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 , wherein the $-\text{C}_{1-6}$ alkyl group is optionally unsaturated;

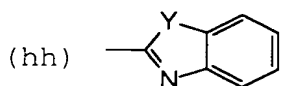
10 each R_{11} is independently selected from the group consisting of:

$-\text{Ar}_4$,
 $-(\text{CH}_2)_{1-3}-\text{Ar}_4$,
 $-\text{H}$, and
 $-\text{C}(\text{O})-\text{Ar}_4$;

15 R_{15} is selected from the group consisting of $-\text{OH}$, $-\text{OAr}_3$, $-\text{N}(\text{H})-\text{OH}$, and $-\text{OC}_{1-6}$, wherein C_{1-6} is a straight or branched alkyl group optionally substituted with $-\text{Ar}_3$, $-\text{CONH}_2$, $-\text{OR}_5$, $-\text{OH}$, $-\text{OR}_9$, or $-\text{CO}_2\text{H}$;

R_{21} is $-\text{H}$ or $-\text{CH}_3$;

20 Ar_2 is:



wherein Y is O ;

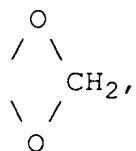
25 each Ar_3 is a cyclic group independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl,

- 242 -

isoxazolyl, benzotriazolyl, benzimidazolyl,
 thienothienyl, imidazolyl, thiadiazolyl,
 benzo[b]thiophenyl, pyridyl benzofuranyl, and indolyl,
 and said cyclic group optionally being singly or
 5 multiply substituted by $-Q_1$;

each Ar_4 is a cyclic group independently selected
 from the set consisting of phenyl, tetrazolyl,
 pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and
 thienyl, and said cyclic group optionally being singly
 10 or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group
 consisting of $-NH_2$, $-Cl$, $-F$, $-Br$, $-OH$, $-R_9$, $-NH-R_5$
 wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is
 15 $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and



20 provided that when $-Ar_3$ is substituted with a Q_1
 group which comprises one or more additional $-Ar_3$
 groups, said additional $-Ar_3$ groups are not substituted
 with another $-Ar_3$;

provided that when:

25 m is 1;
 R_{15} is $-OH$;
 R_{21} is $-H$; and

Y_2 is O and R_3 is $-C(O)-H$, then R_5 cannot be:
 $-C(O)-R_{10}$, wherein R_{10} is $-Ar_3$ and the Ar_3 cyclic

- 243 -

group is phenyl, unsubstituted by $-Q_1$, 4-(carboxymethoxy)phenyl, 2-fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

5 $-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$, and the Ar_3 cyclic group is phenyl, unsubstituted by $-Q_1$; and when

Y_2 is O, R_3 is $-C(O)-CH_2-T_1-R_{11}$, T_1 is O, and R_{11} is Ar_4 , wherein the Ar_4 cyclic group is 5-(1-(4-chlorophenyl)-3-trifluoromethyl)pyrazolyl), then R_5 cannot be:

10 $-H$;

$-C(O)-R_{10}$, wherein R_{10} is $-Ar_3$ and the Ar_3 cyclic group is 4-(dimethylaminomethyl)phenyl, phenyl, 4-(carboxymethylthio)phenyl, 4-(carboxyethylthio)phenyl, 4-(carboxyethyl)phenyl, 4-(carboxypropyl)phenyl, 2-fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

15

$-C(O)-OR_9$, wherein R_9 is isobutyl or $-CH_2-Ar_3$ and the Ar_3 cyclic group is phenyl;

and when R_{11} is Ar_4 , wherein the Ar_4 cyclic group is 5-(1-phenyl-3-trifluoromethyl)pyrazolyl or 5-(1-(4-chloro-2-pyridinyl)-3-trifluoromethyl)pyrazolyl, then R_5 cannot be:

20

$-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$, and the Ar_3 cyclic group is phenyl;

25 and when R_{11} is Ar_4 , wherein the Ar_4 cyclic group is 5-(1-(2-pyridyl)-3-trifluoromethyl)pyrazolyl), then R_5 cannot be:

$-C(O)-R_{10}$, wherein R_{10} is $-Ar_3$ and the Ar_3 cyclic group is 4-(dimethylaminomethyl)phenyl, or

30

$-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$, and the Ar_3 cyclic group is phenyl, unsubstituted by $-Q_1$; and when

- 244 -

Y_2 is O, R_3 is $-C(O)-CH_2-T_1-R_{11}$, T_1 is O, and R_{11} is $-C(O)-Ar_4$, wherein the Ar_4 cyclic group is 2,5-dichlorophenyl, then R_5 cannot be:

5 $-C(O)-R_{10}$, wherein R_{10} is $-Ar_3$ and the Ar_3 cyclic group is 4-(dimethylaminomethyl)phenyl, 4-(N-morpholinomethyl)phenyl, 4-(N-methylpiperazino)methyl)phenyl, 4-(N-(2-methylimidazolylmethyl)phenyl, 5-benzimidazolyl, 5-benzotriazolyl, N-carboethoxy-5-benzotriazolyl, N-
10 carboethoxy-5-benzimidazolyl, or
 $-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$, and the Ar_3 cyclic group is phenyl, unsubstituted by $-Q_1$,; and when

Y_2 is H_2 , R_3 is $-C(O)-CH_2-T_1-R_{11}$, T_1 is O, and R_{11} is $-C(O)-Ar_4$, wherein the Ar_4 cyclic group is 2,5-dichlorophenyl, then R_5 cannot be:

15 $-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$ and the Ar_3 cyclic group is phenyl.

Preferably, in any of the above compounds of embodiment (L), R_3 is $-C(O)-H$ and R_5 is $-C(O)-R_{10}$ or
20 $-C(O)-C(O)-R_{10}$ and the other substituents are as defined above.

More preferably R_{10} is $-Ar_3$ and the other substituents are as defined above.

25 More preferably in these more preferred compounds:

R_5 is $-C(O)-R_{10}$ and R_{10} is Ar_3 , wherein the Ar_3 cyclic group is phenyl optionally being singly or multiply substituted by:

30 $-R_9$, wherein R_9 is a C_{1-4} straight or branched alkyl group;

$-F$,

$-Cl$,

$-N(H)-R_5$, wherein $-R_5$ is $-H$ or $-C(O)-R_{10}$,

- 245 -

wherein R_{10} is a $-C_{1-6}$ straight or branched alkyl group optionally substituted with Ar_3 , wherein Ar_3 is phenyl,

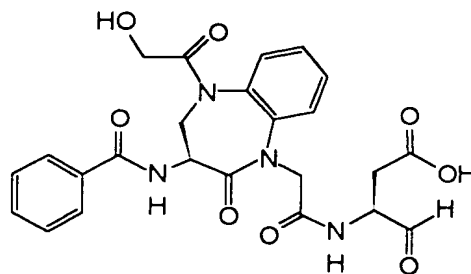
5 $-N(R_9)(R_{10})$, wherein R_9 and R_{10} are independently a $-C_{1-4}$ straight or branched alkyl group, or

$-O-R_5$, wherein R_5 is H or a $-C_{1-4}$ straight or branched alkyl group.

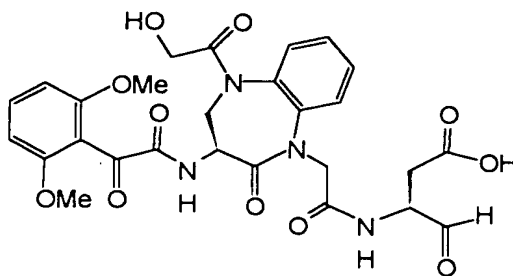
Preferred compounds of this preferred embodiment include, but are not limited to:

10

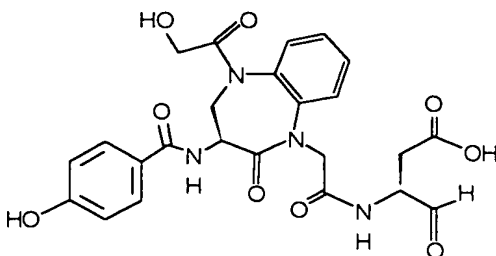
668



678

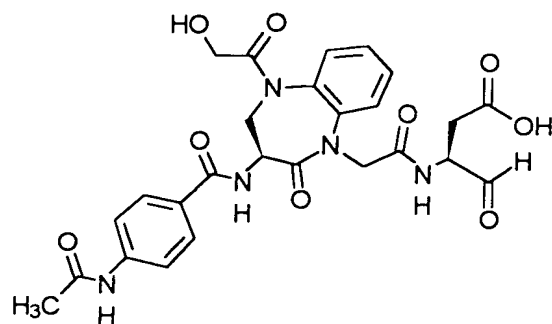


691b



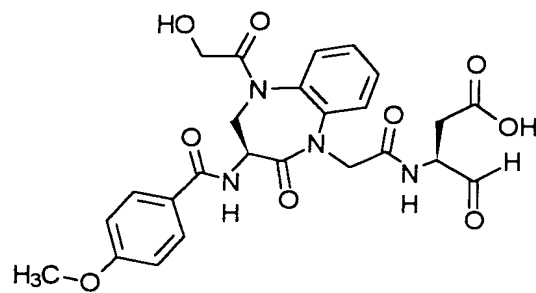
- 246 -

911



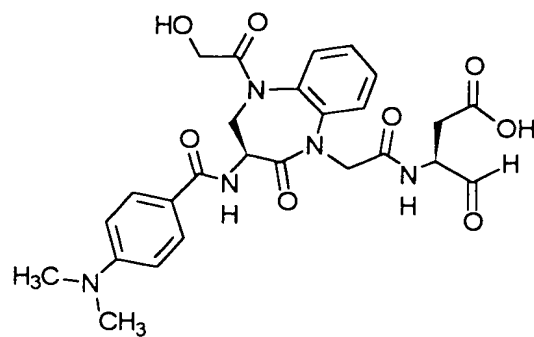
;

912



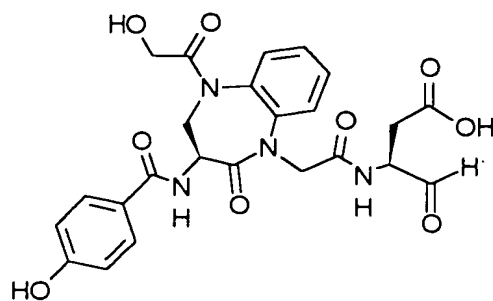
;

913



; and

916

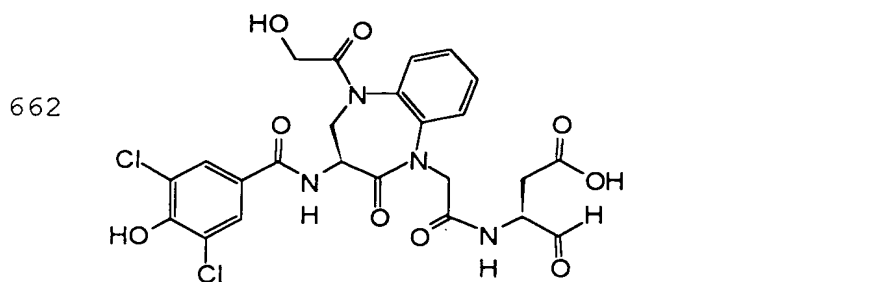
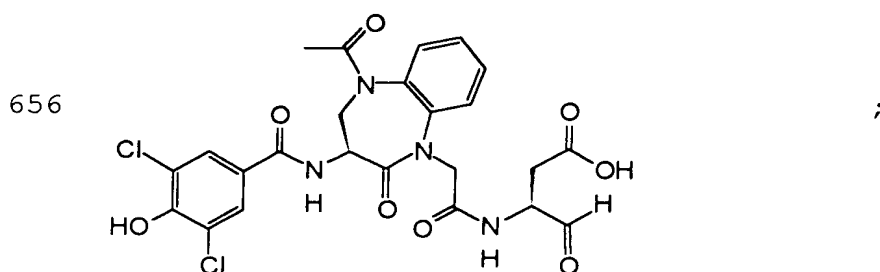


- 247 -

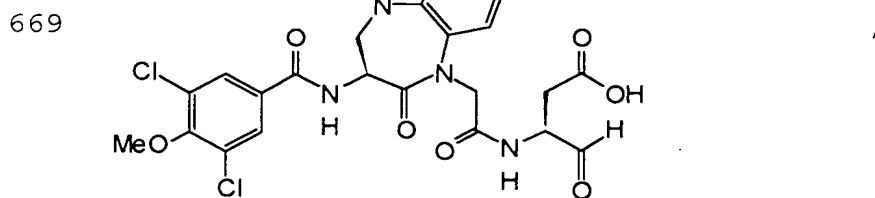
Most preferably, Ar_3 is phenyl being singly or multiply substituted at the 3- or 5-position by $-Cl$ or at the 4-position by $-NH-R_5$, $-N(R_9)(R_{10})$, or $-O-R_5$.

5

Preferred compounds of this most preferred embodiment include, but are not limited to:

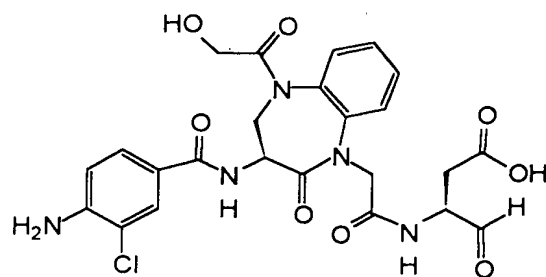


10

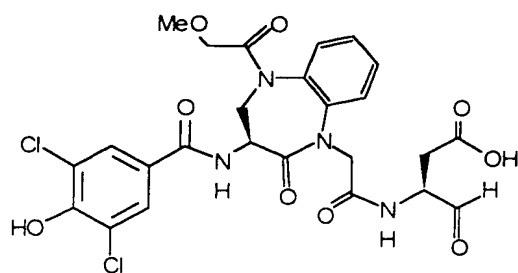


- 248 -

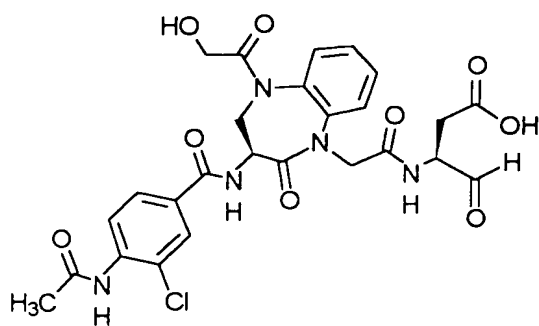
686



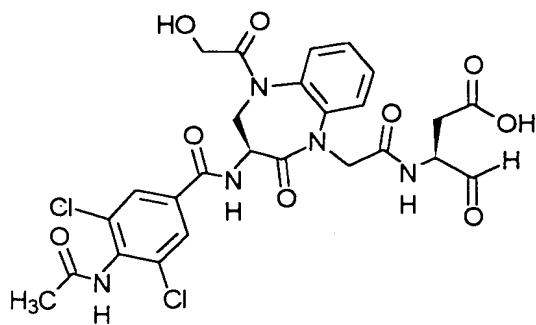
689a



914



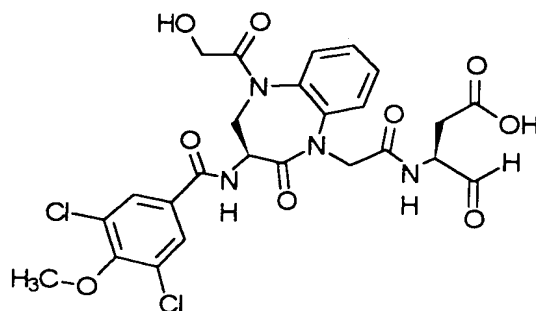
915



; and

- 249 -

918

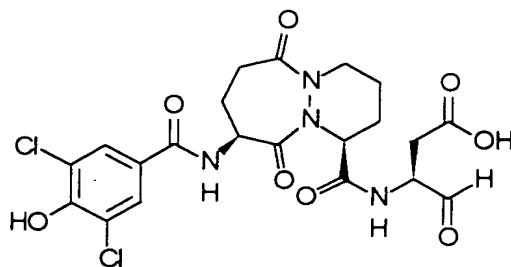


Other preferred compounds of this most preferred embodiment include, but are not limited to:

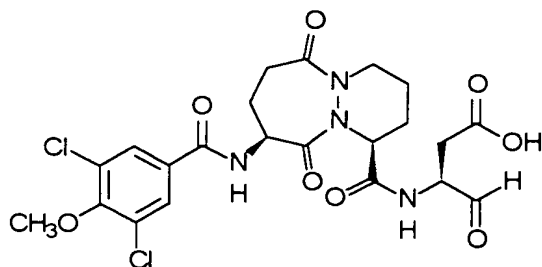
5

214k

; and



214m



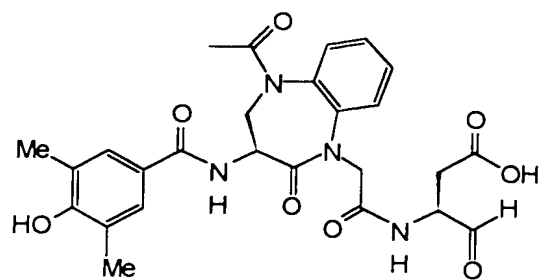
10

Alternatively, Ar₃ is phenyl being singly or multiply substituted at the 3- or 5-position by -R₉, wherein R₉ is a C₁₋₄ straight or branched alkyl group; and at the 4-position by -O-R₅.

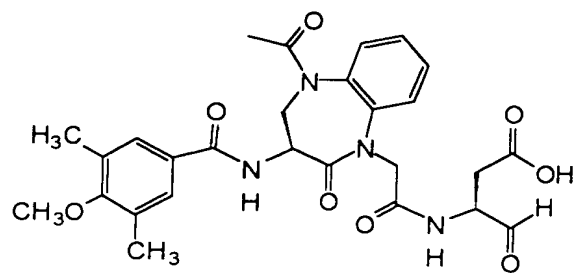
Preferred compounds of this most preferred embodiment include, but are not limited to:

- 250 -

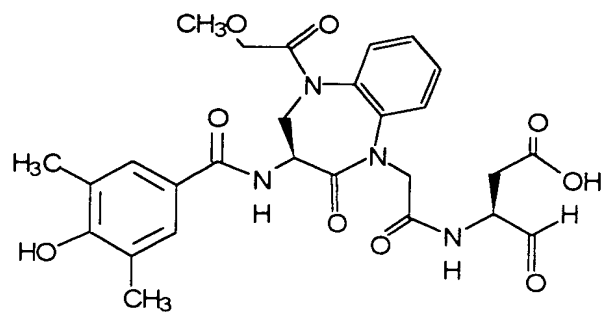
671



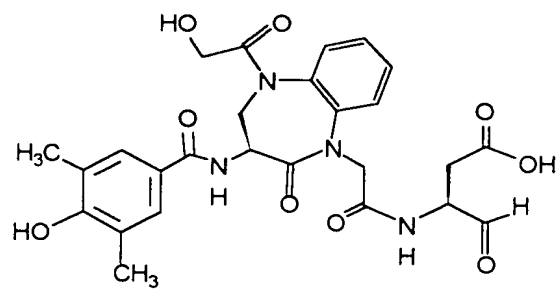
684



689b

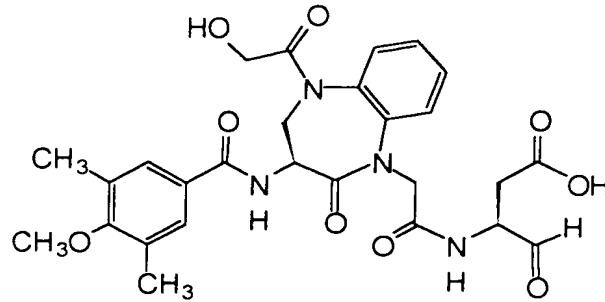


691a



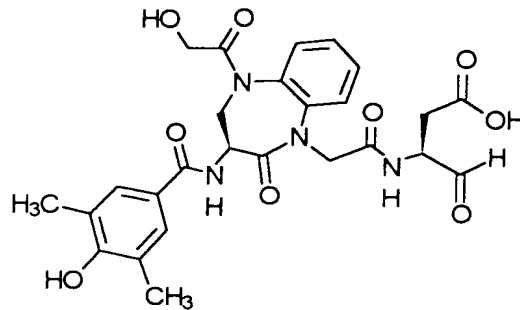
- 251 -

694



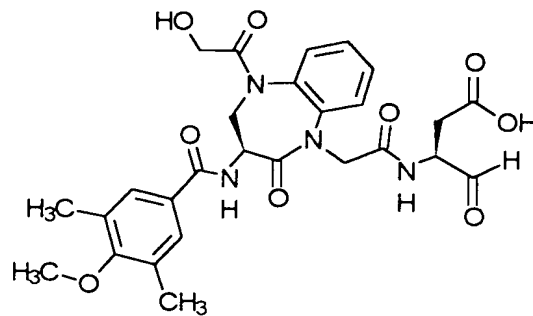
;

917



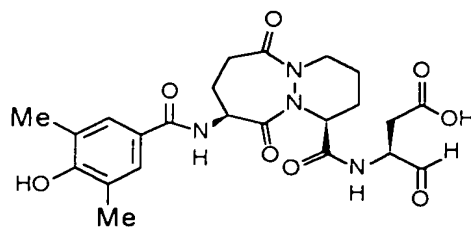
; and

922



Another preferred compound of
 5 this most preferred embodiment includes, but is not
 limited to:

214w

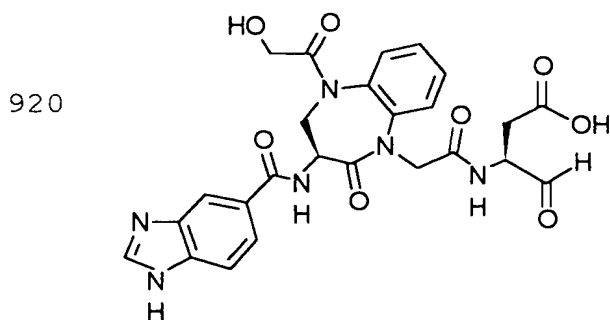
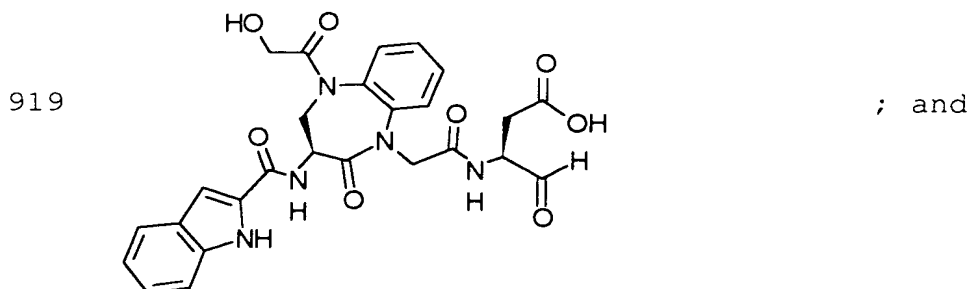


- 252 -

Alternatively, in this more preferred embodiment:

5 R_5 is $-C(O)-R_{10}$, wherein R_{10} is Ar_3 and the Ar_3 cyclic group is selected from the group consisting of is indolyl, benzimidazolyl, thienyl, quinolyl, isoquinolyl and benzo[b]thiophenyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$.

10 Preferred compounds of this more preferred embodiment include, but are not limited to:



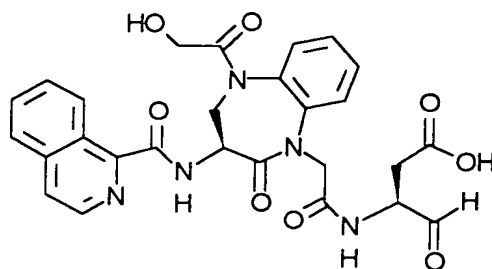
15 Most preferably, the Ar_3 cyclic group is isoquinolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$.

A preferred compound of this most preferred embodiment includes, but is not limited

- 253 -

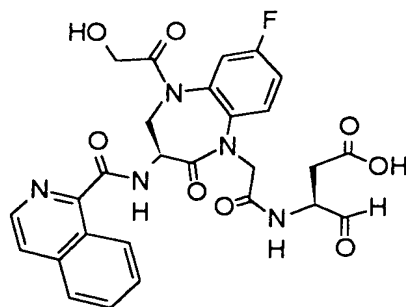
to:

696



;

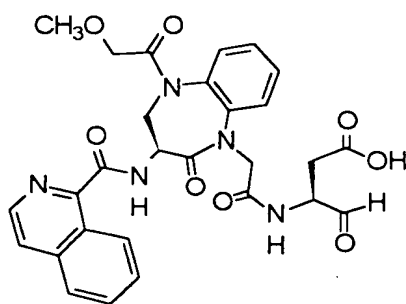
696-1



; and

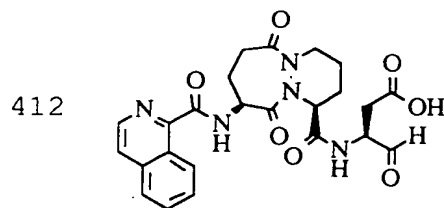
5

699

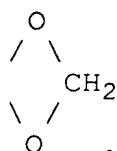


Another preferred compound of this most preferred embodiment includes, but is not limited to:

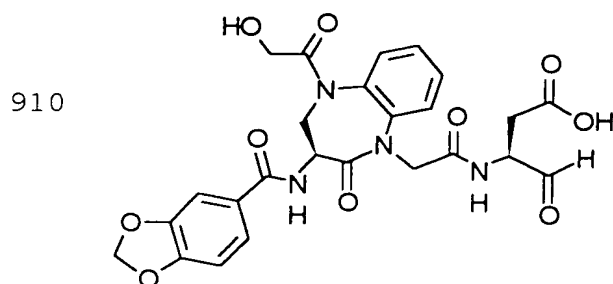
- 254 -



Alternatively, in this more preferred embodiment R_5 is $-C(O)-R_{10}$, wherein R_{10} is $-Ar_3$ and the Ar_3 cyclic group is phenyl, substituted by



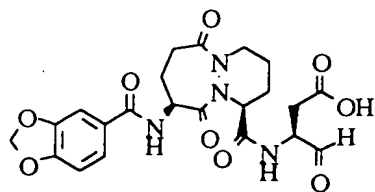
A preferred compound of this more preferred embodiment includes, but is not limited to:



15 A preferred compound of this more preferred embodiment includes, but is not limited to:

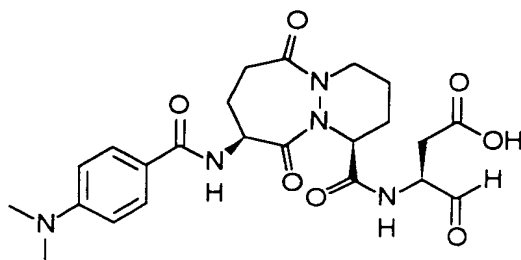
- 255 -

415



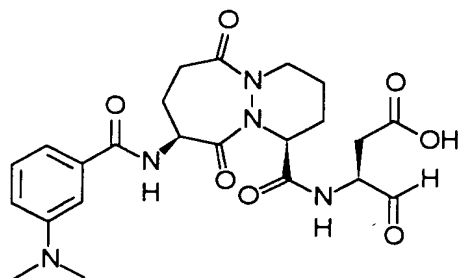
Other compounds of embodiment (L) include,
but are not limited to:

214f

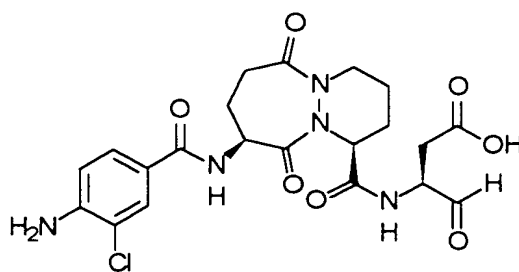


5

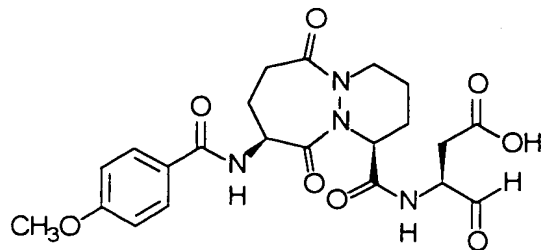
214g



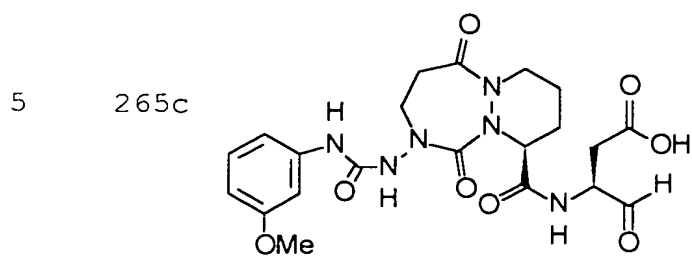
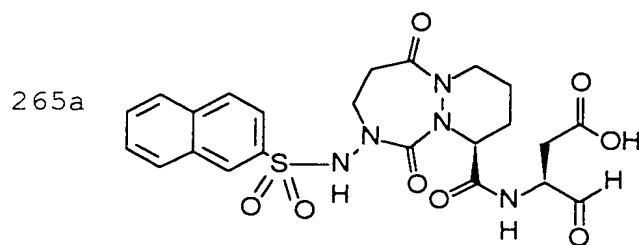
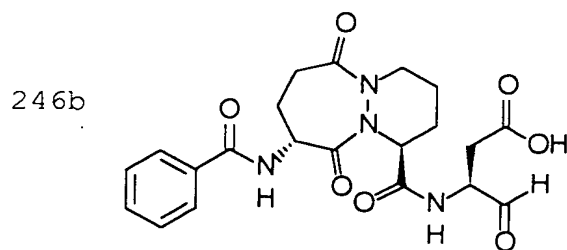
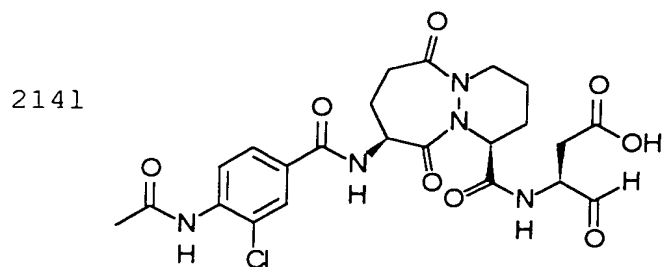
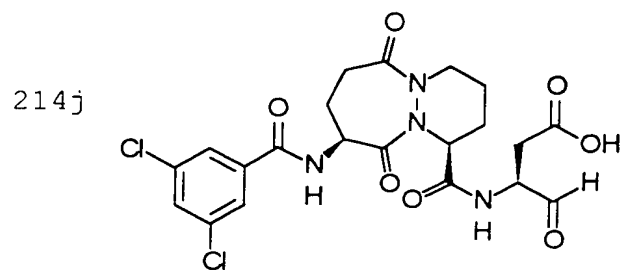
214h



214i

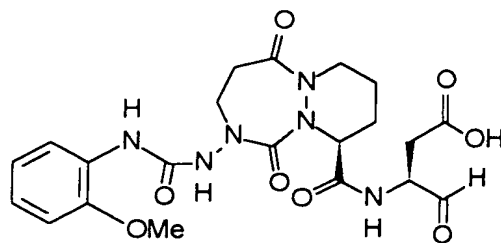


- 256 -



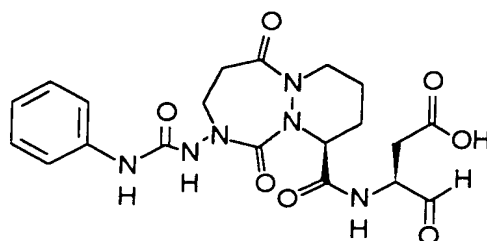
- 257 -

265d



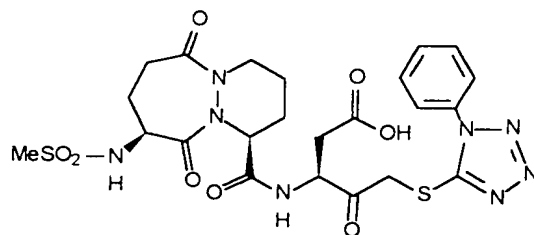
;

265f



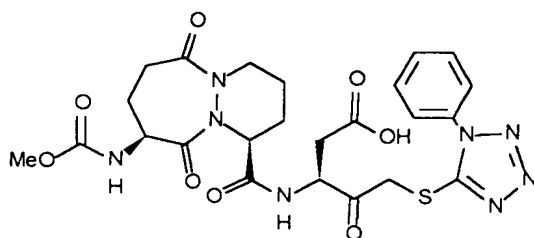
;

280b



;

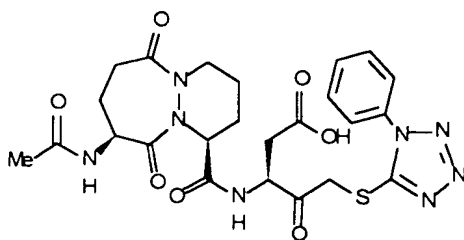
280c



;

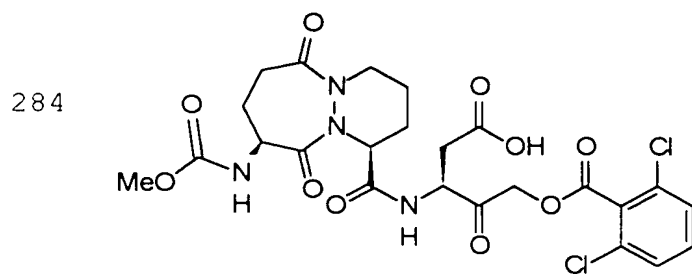
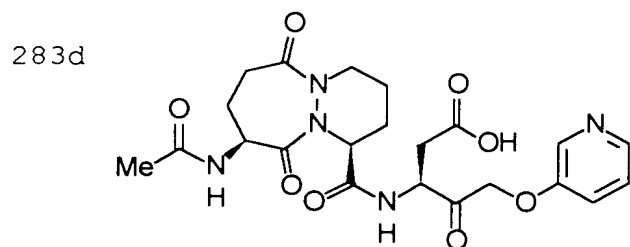
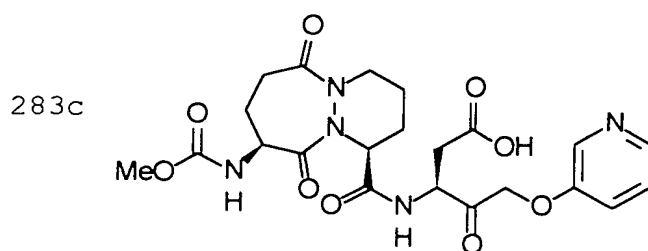
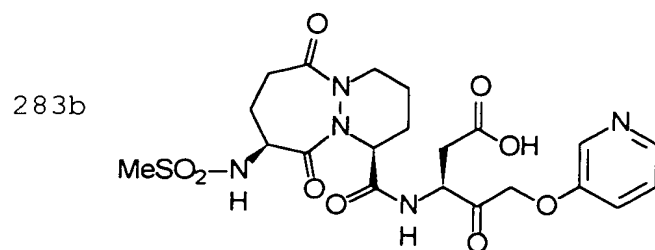
5

280d

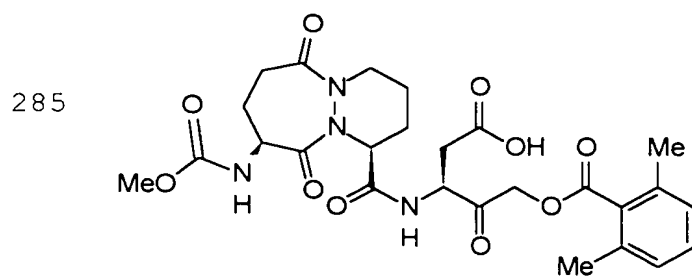


;

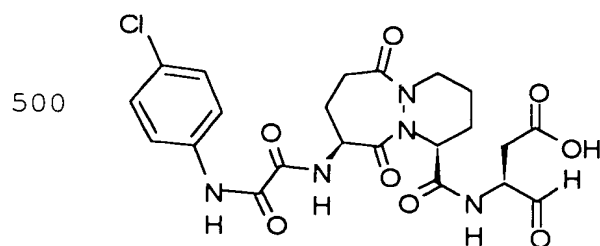
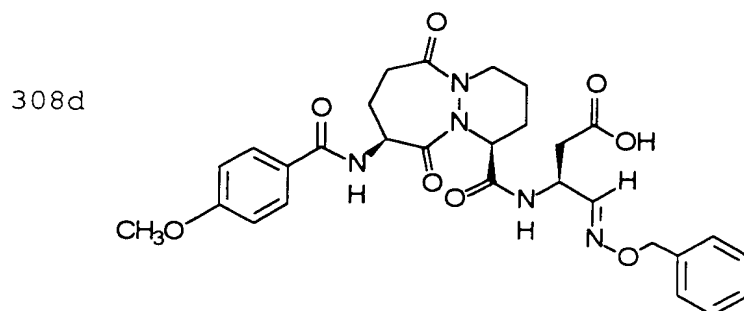
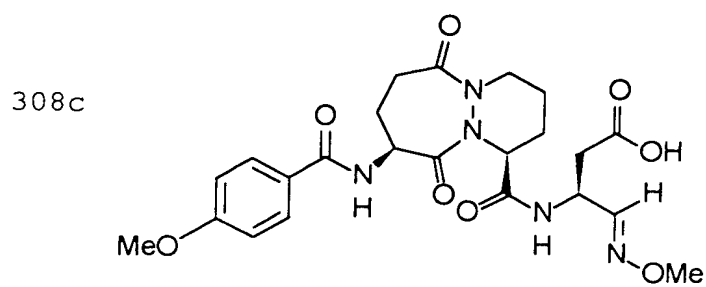
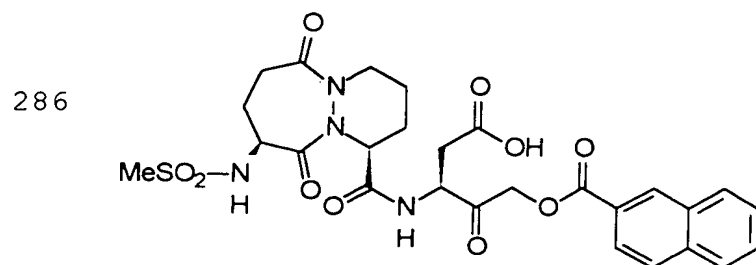
- 258 -



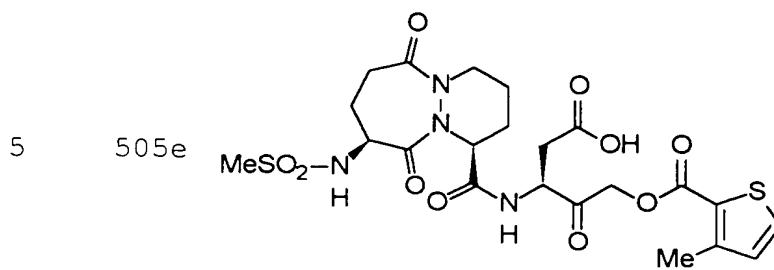
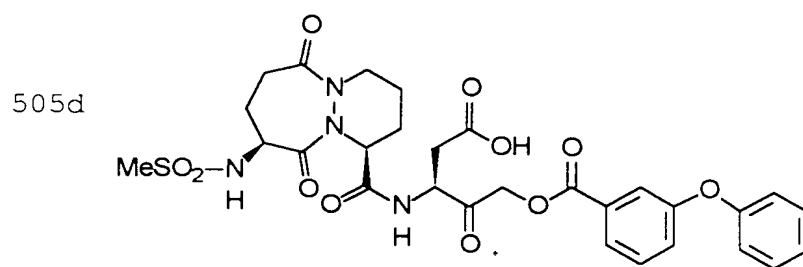
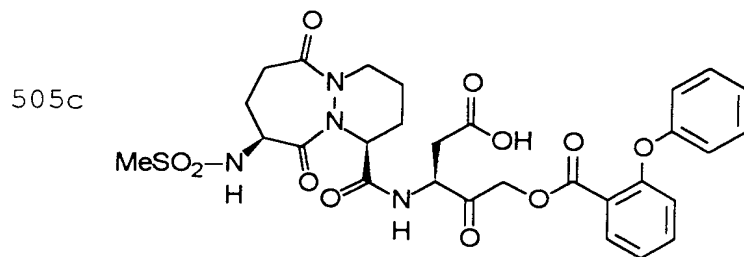
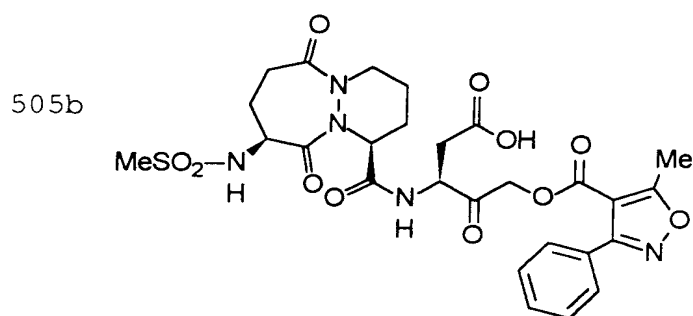
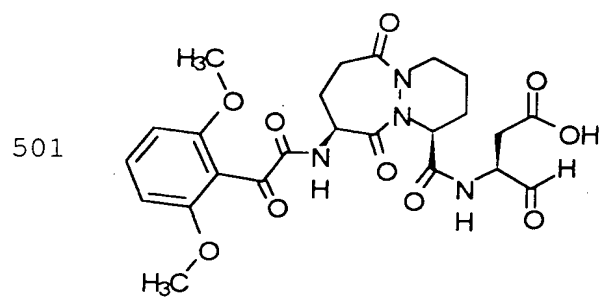
5



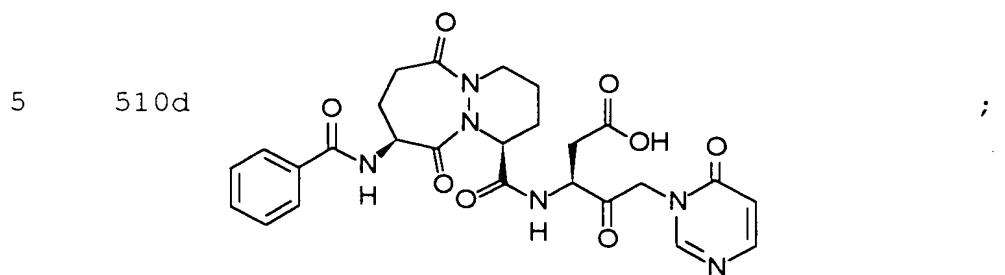
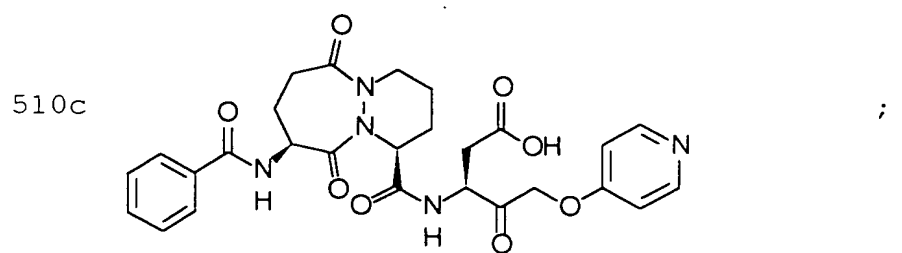
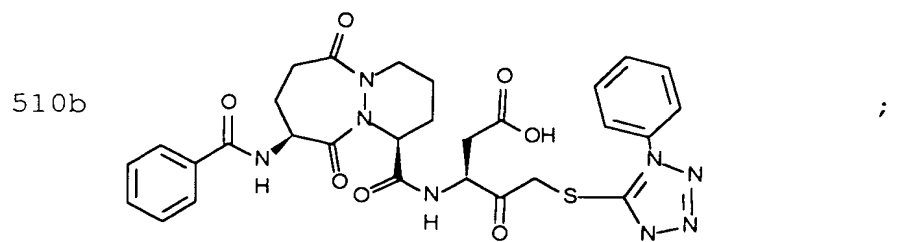
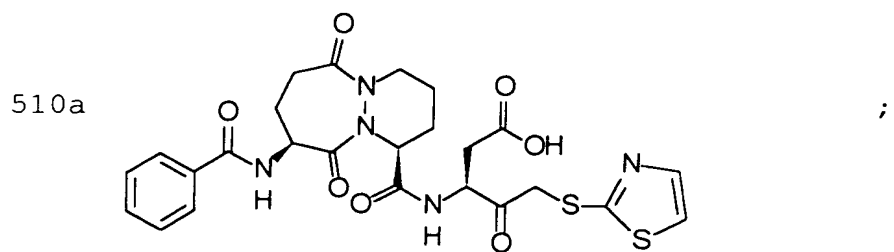
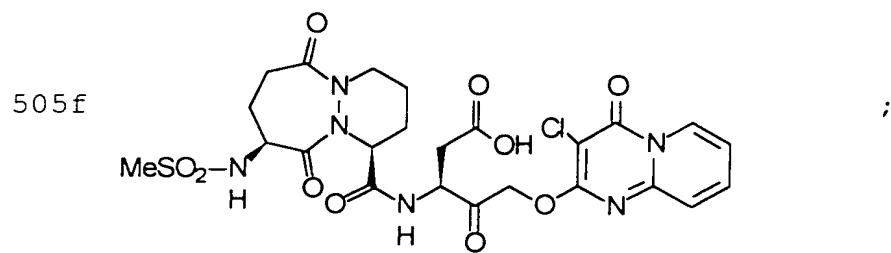
- 259 -



- 260 -

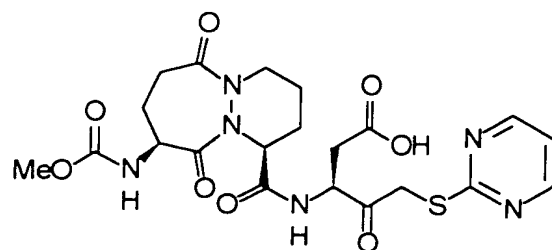


- 261 -



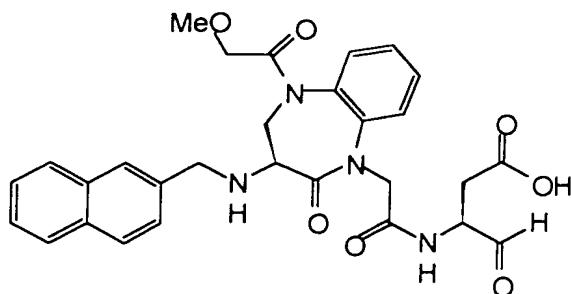
- 262 -

511c



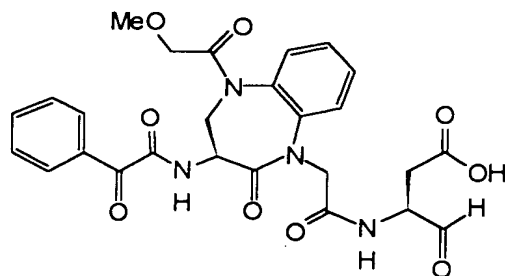
;

640



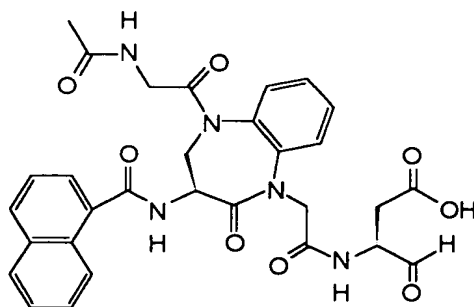
;

642



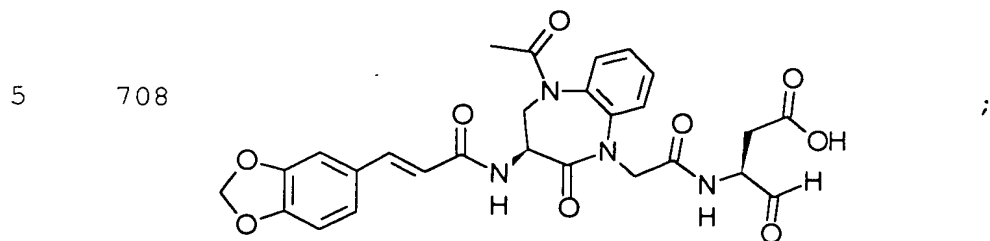
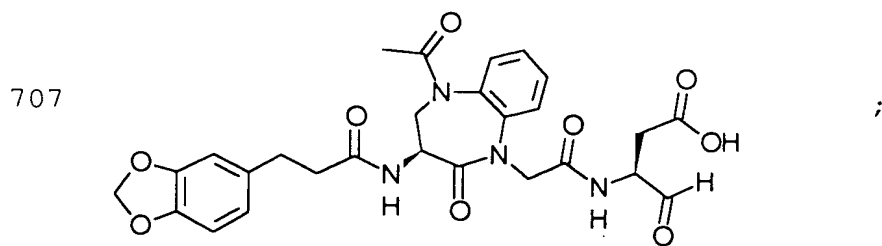
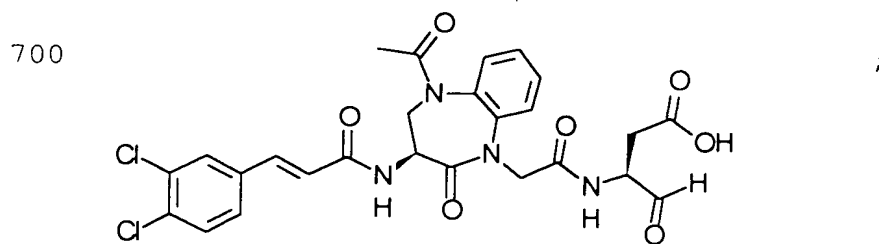
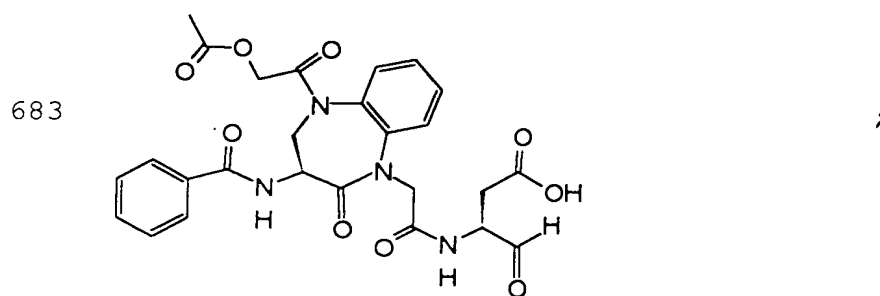
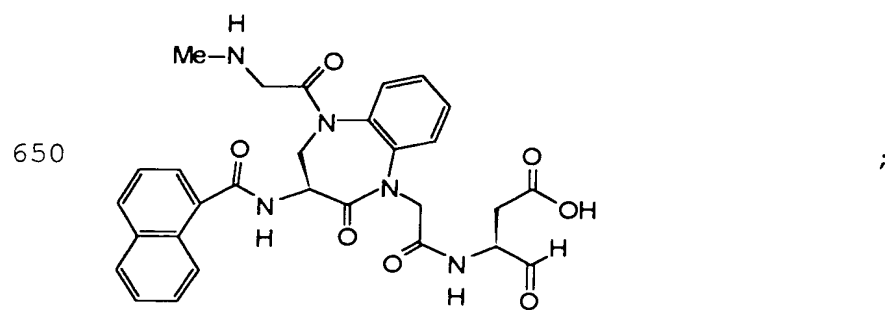
;

645



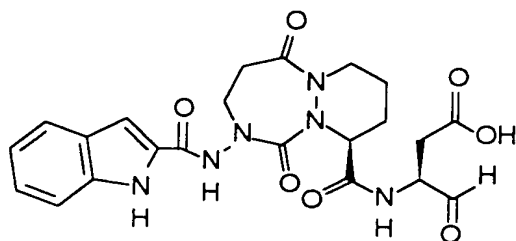
;

- 263 -



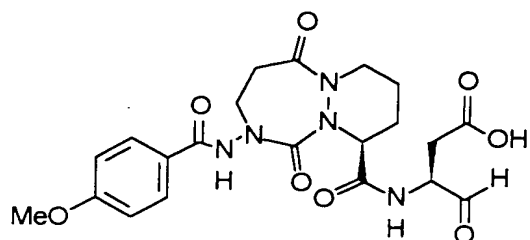
- 264 -

1018



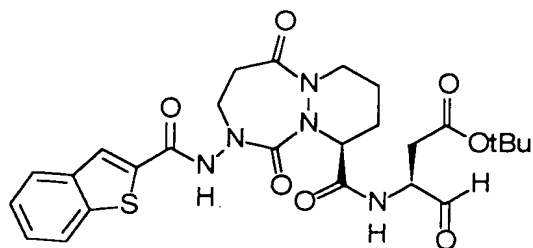
;

1052



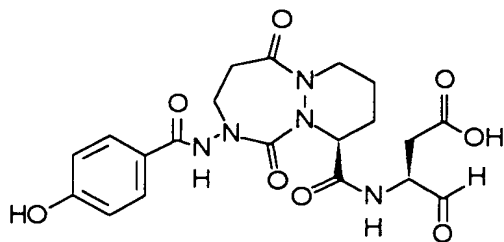
;

1053



;

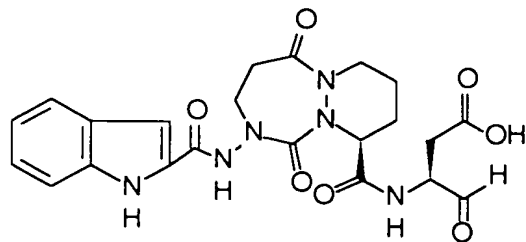
1056



;

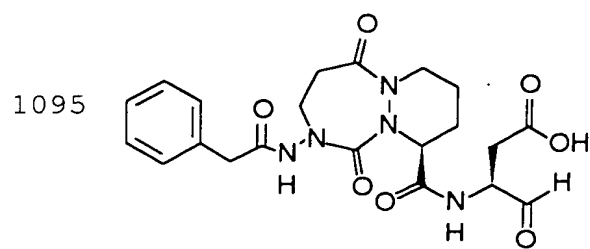
5

1075

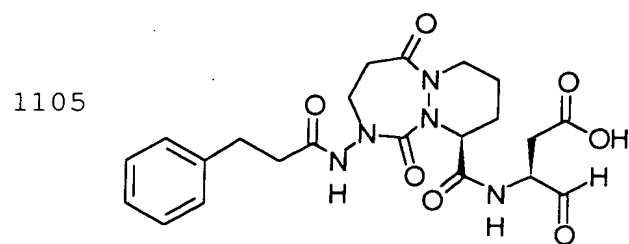


;

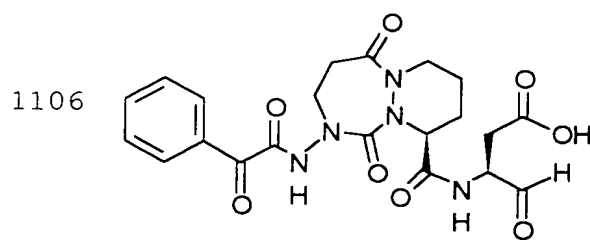
- 265 -



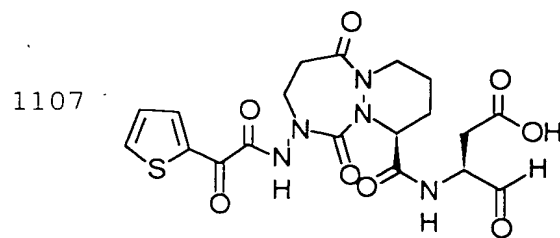
;



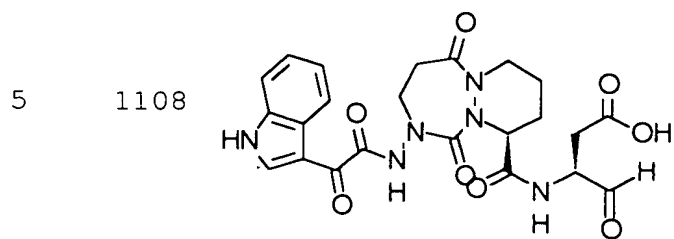
;



;



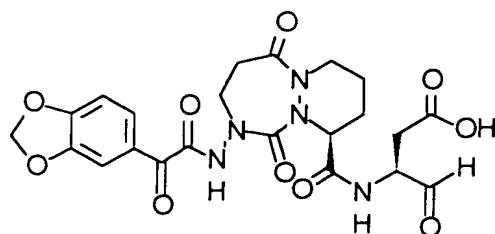
;



;

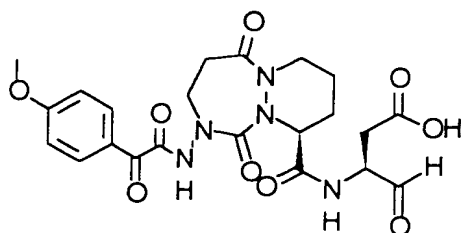
- 266 -

1109



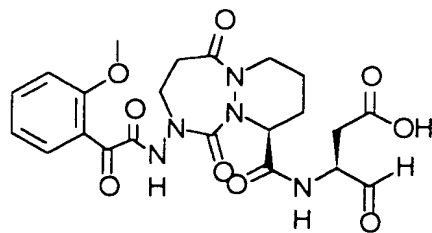
;

1110



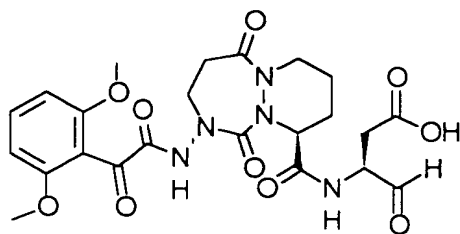
i

1111



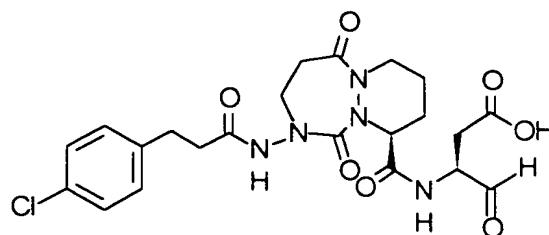
i

1112

*i*

5

1113

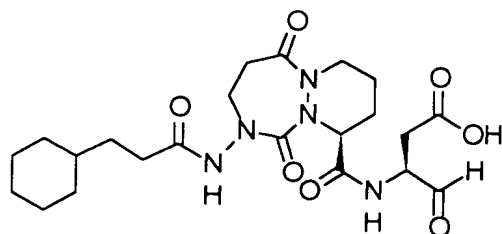


i

O=C(O)[C@H](NC(=O)[C@@H]1CCN2C(=O)N(C(=O)N2CCC1)C(=O)NCCC1c3ccc4c(c3)OCO4)C(=O)OO=C(O)[C@H](NC(=O)N1C(=O)N2C(=O)N(CCN2C1=O)C3=CC=C(C=C3C4=CC(=CC=C4)C(=O)O)C5=CC(=CC=C5)C(=O)O)C6=CC(=CC=C6)C(=O)OO=C(O)[C@H](NC(=O)N1CC[C@@]2(CCN1C(=O)N2C(=O)N/C=C/c3ccc4c(c3)OCO4)C(=O)O)C(=O)OCc1cc(C)c(C)c(C(=O)N2CC3C(=O)N2CC4C(=O)N3C[C@H](C4)C(=O)O)c1O=C(O)[C@H](N1C(=O)N2C(=O)N(C1)C(=O)N2C(=O)N3CCCCC3)C(=O)O

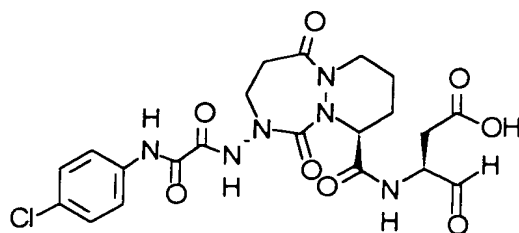
- 268 -

1119



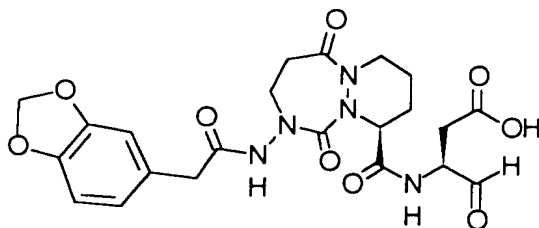
;

1120



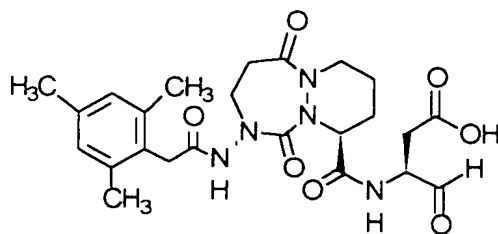
;

1121



;

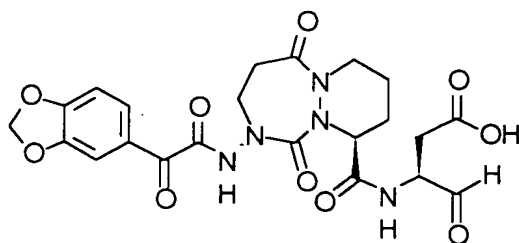
1122



;

5

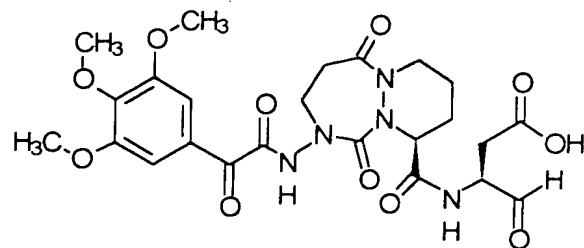
1123



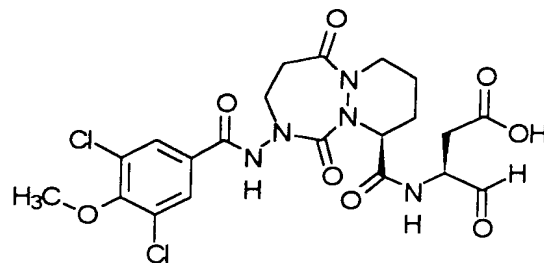
;

- 269 -

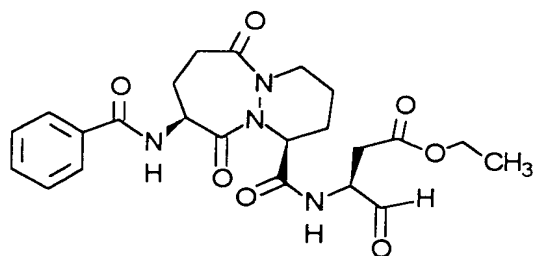
1124



1125

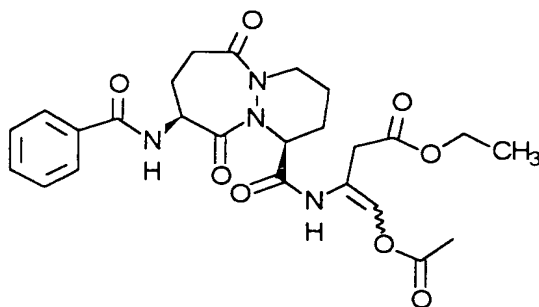


2100i



5

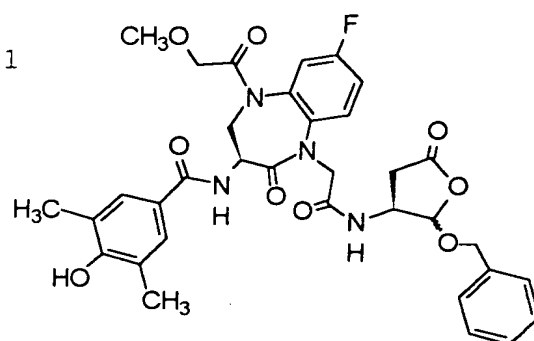
2100j



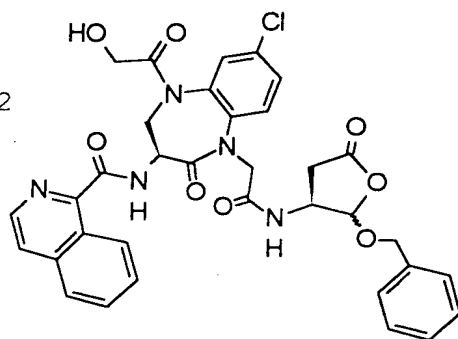
Other compounds of embodiment (K) include,
but are not limited to:

- 270 -

688b-1

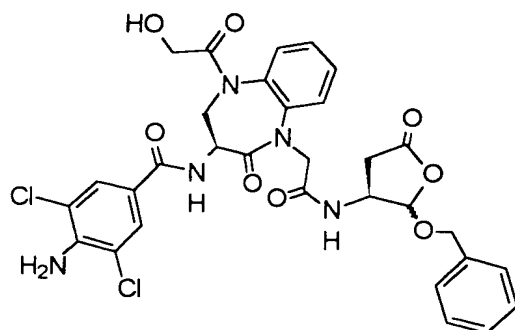


696a-2

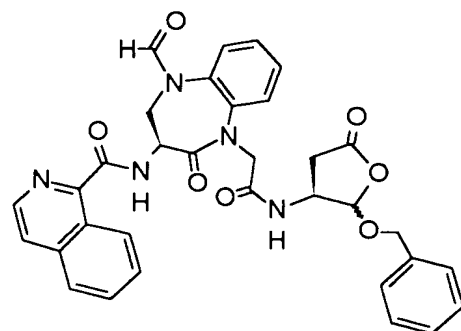


5

697a

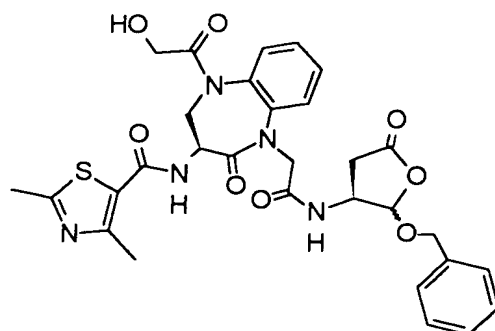


698a



- 271 -

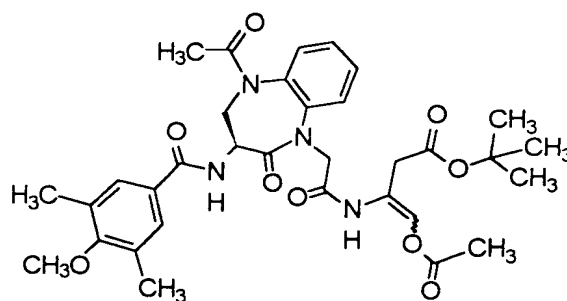
800



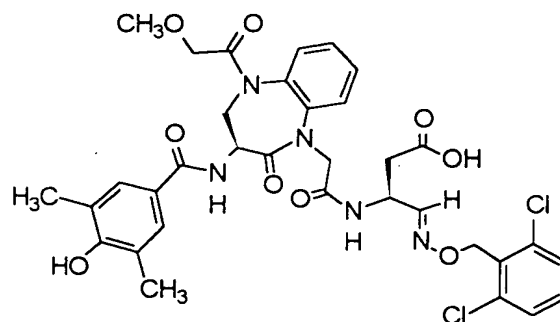
Other compounds of embodiment (L) include, but are not limited to:

5

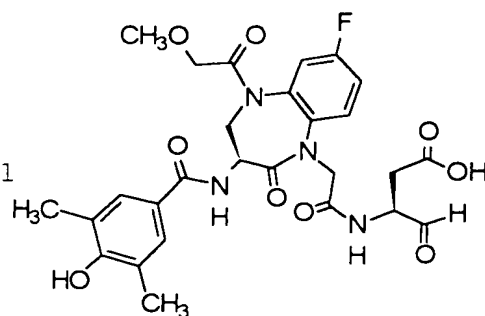
684a



688c



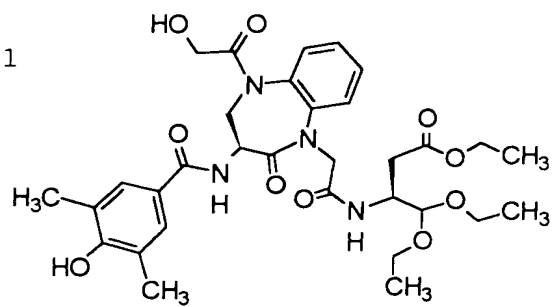
689b-1



10

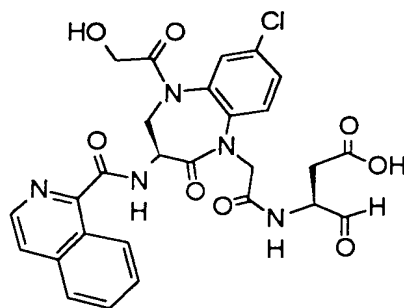
- 272 -

690a-1



;

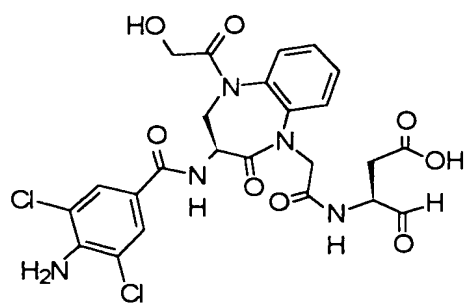
696-2



;

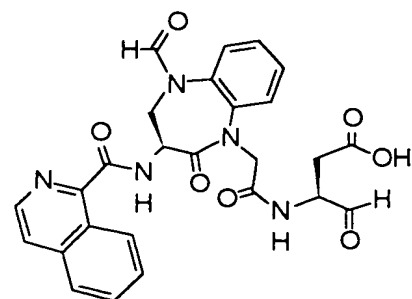
5

697



;

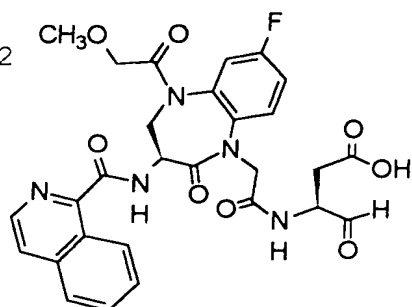
698



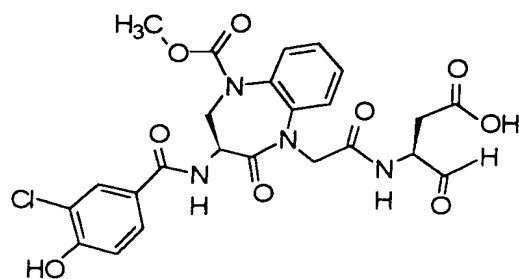
;

- 273 -

699a-2

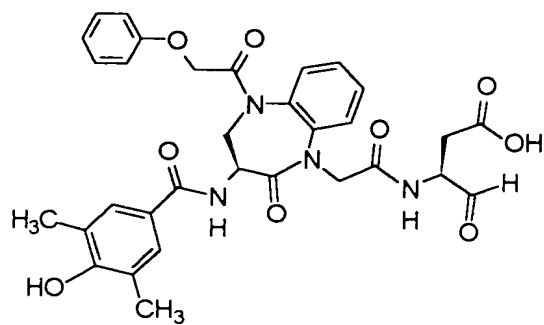


720

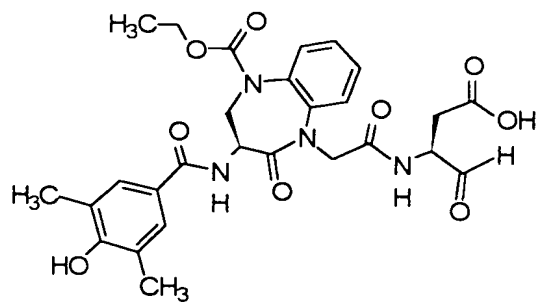


5

721

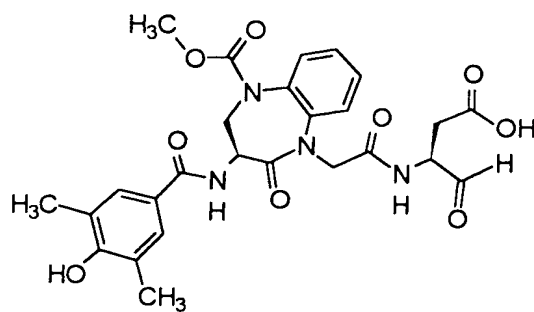


722

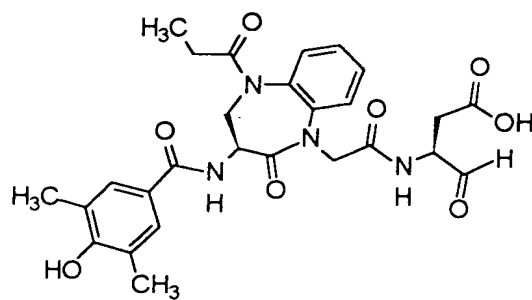


- 274 -

723

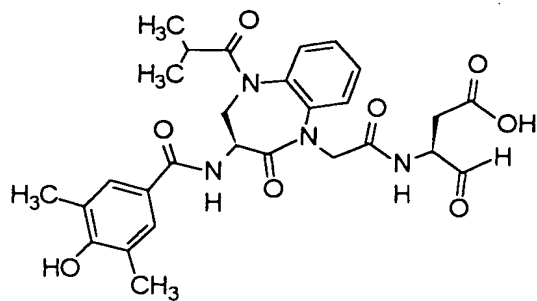


724

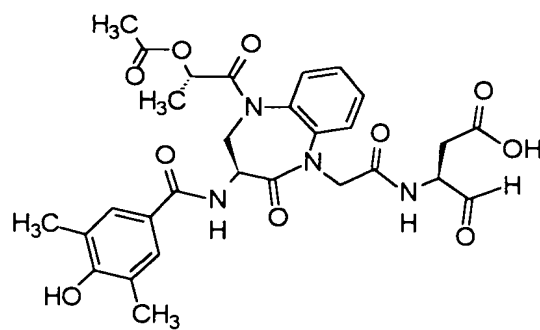


5

725

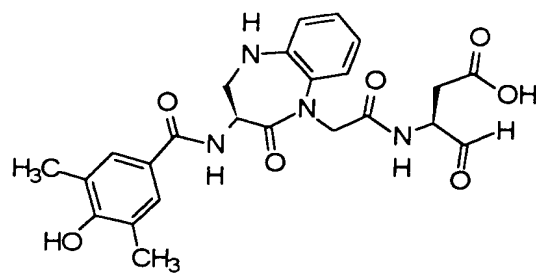


726



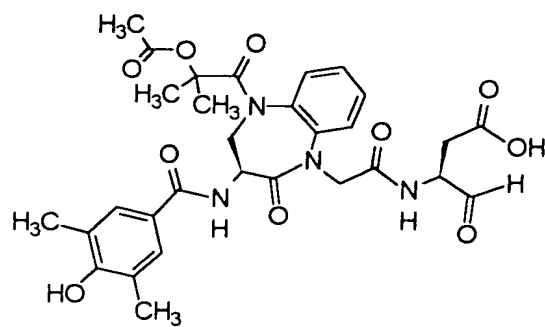
- 275 -

727



;

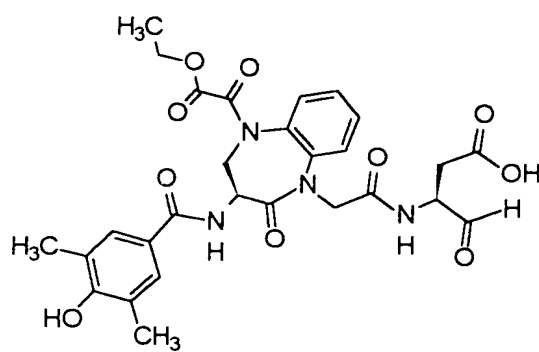
728



;

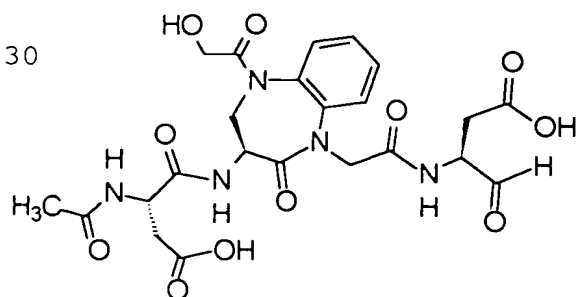
5

729



;

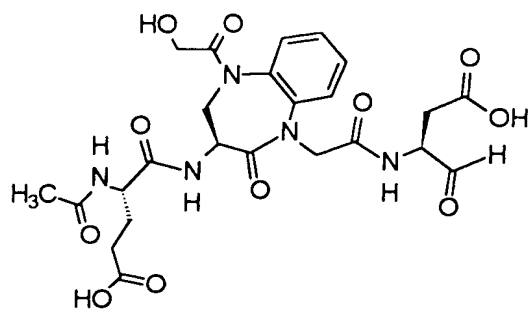
730



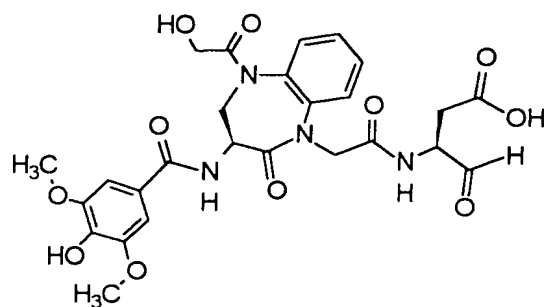
;

- 276 -

731

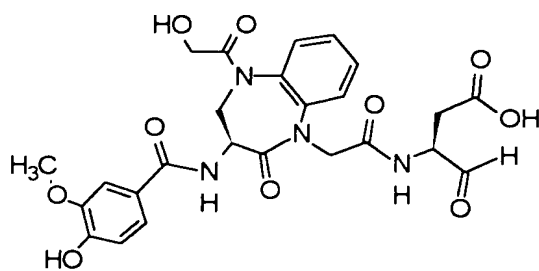


732

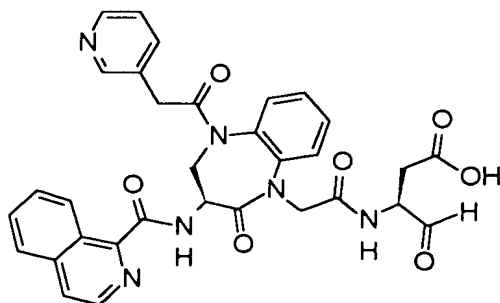


5

733

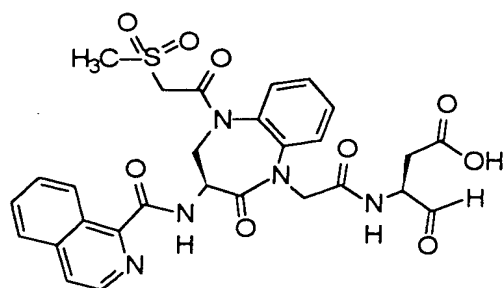


734



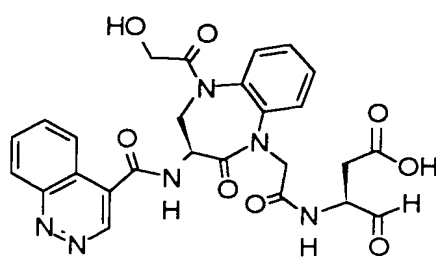
- 277 -

735



;

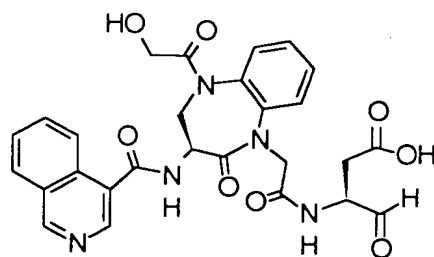
736



;

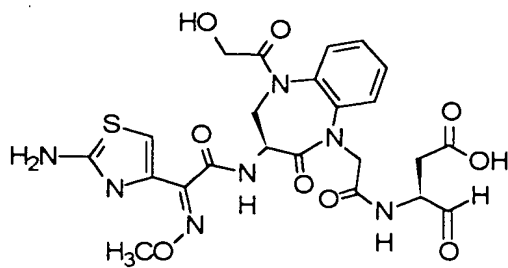
5

737



;

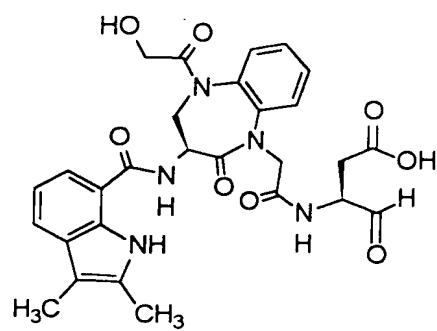
738



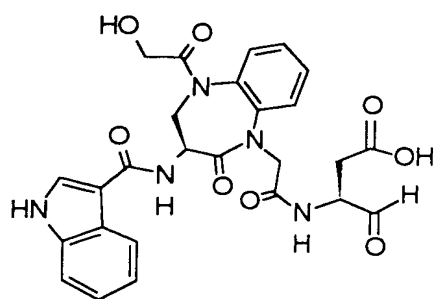
;

- 278 -

739

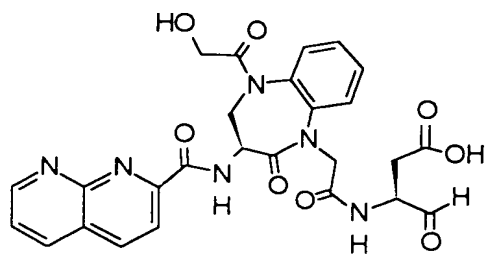


740

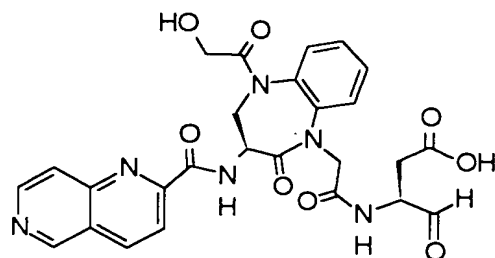


5

741

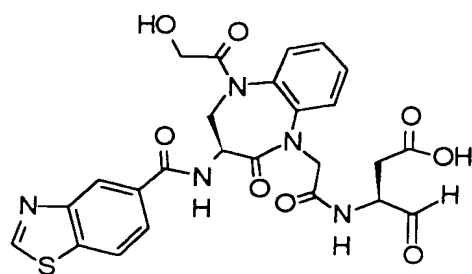


742



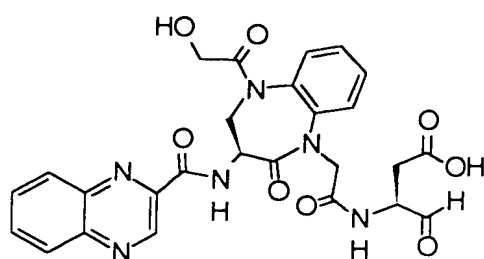
- 279 -

743



;

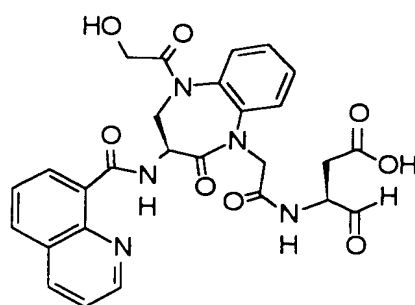
744



;

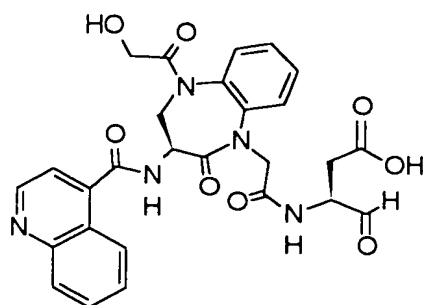
5

745



;

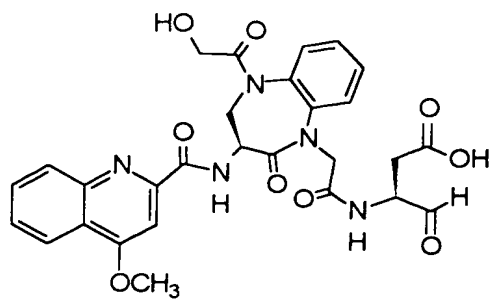
746



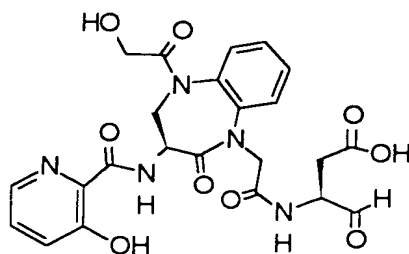
;

- 280 -

747

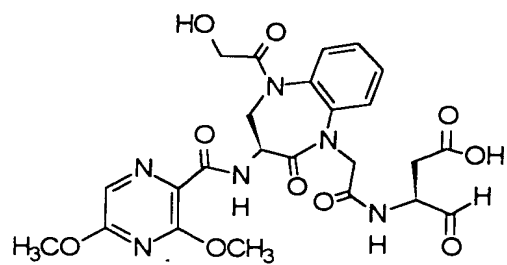


748

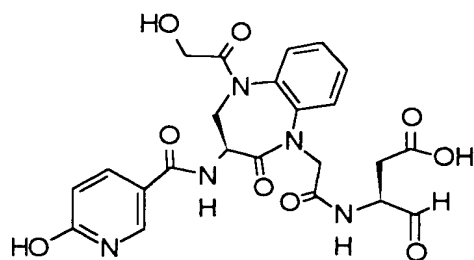


5

749

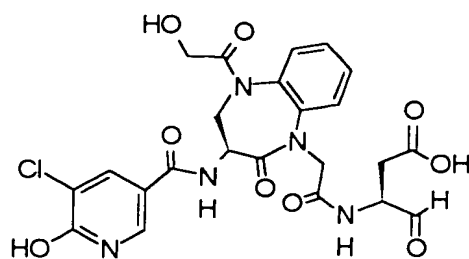


750



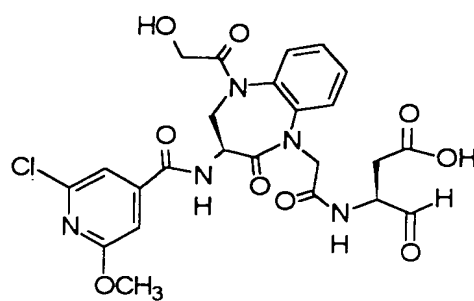
- 281 -

751



;

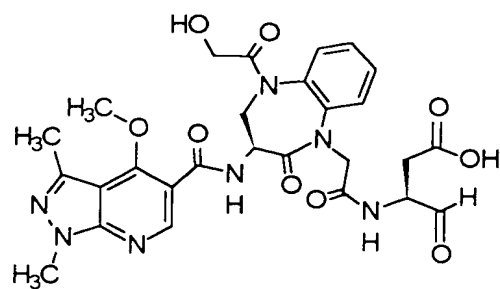
752



;

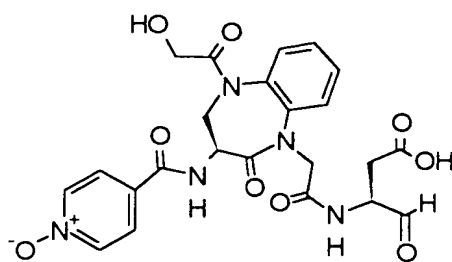
5

753



;

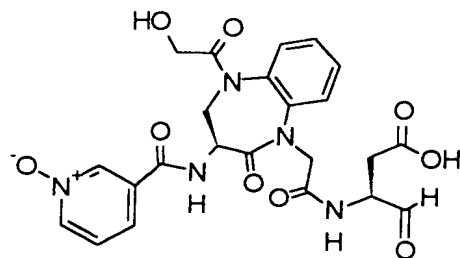
754



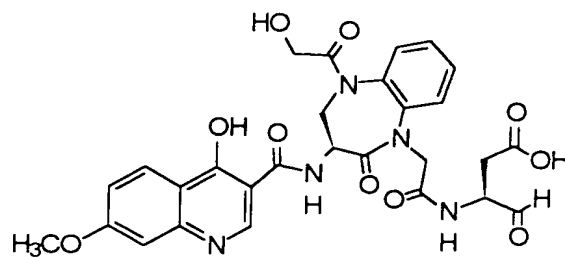
;

- 282 -

755

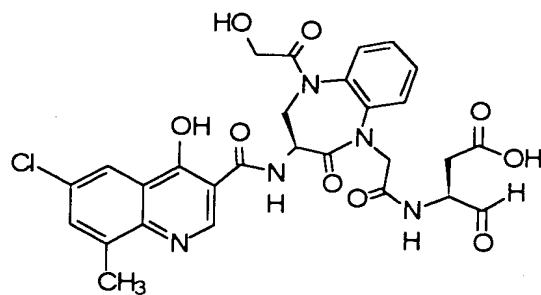


756

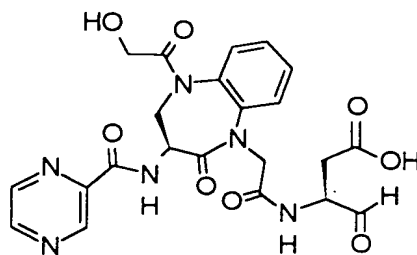


5

757

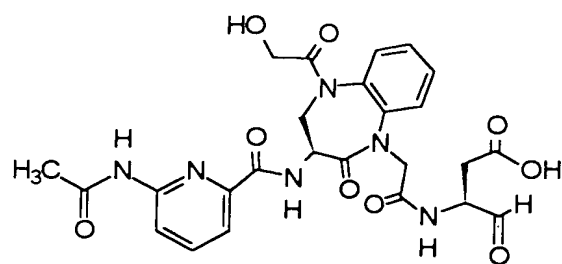


758



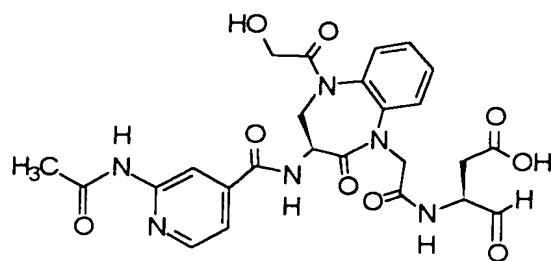
- 283 -

759



;

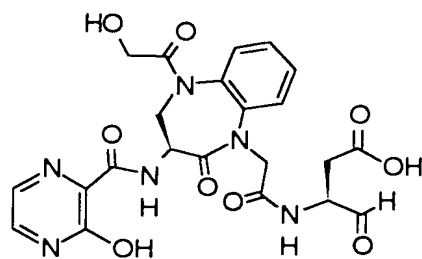
760



;

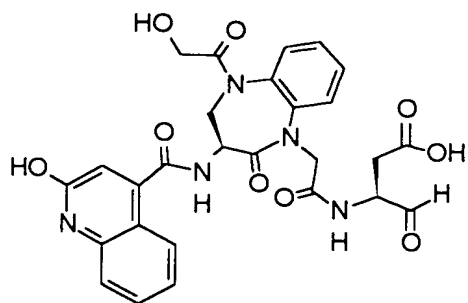
5

761



;

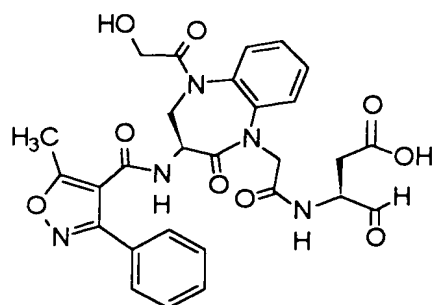
762



;

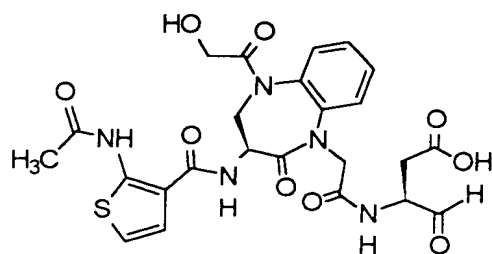
- 284 -

763



;

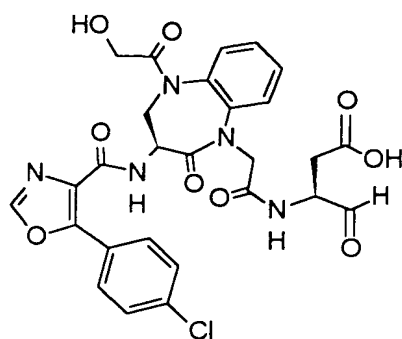
764



;

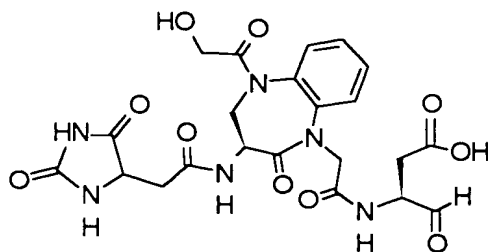
5

765



;

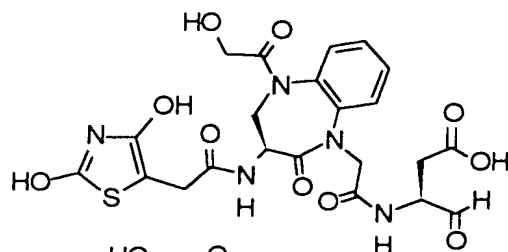
766



;

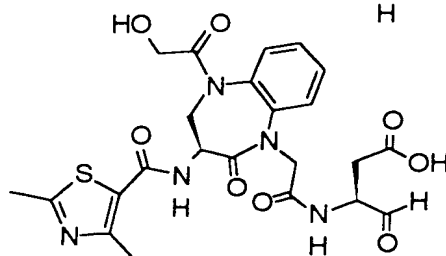
- 285 -

767



; and

801



5

The most preferred compounds of embodiments (K) and (L) are those wherein the Ar₃ cyclic group is isoquinolyl.

10

Compounds of this invention are described in co-pending United States Application Serial Nos. 08/575,641 and 08/598,332 the disclosures of which are herein incorporated by reference.

15

The compounds of this invention have a molecular weight of less than or equal to about 700 Daltons, and more preferably between about 400 and 600 Daltons. These preferred compounds may be readily absorbed by the bloodstream of patients upon oral administration. This oral availability makes such compounds excellent agents for orally-administered treatment and prevention regimens against IL-1-, apoptosis-, IGIF- or IFN- γ mediated diseases.

20

25

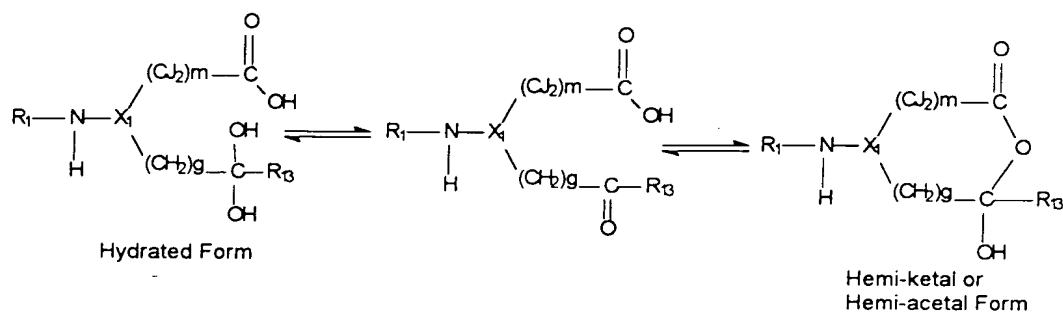
It should be understood that the compounds of this invention may exist in various equilibrium forms, depending on conditions including choice of solvent, pH, and others known to the practitioner skilled in the art. All such forms of these compounds are expressly included in the present invention. In particular, many

- 286 -

of the compounds of this invention, especially those which contain aldehyde or ketone groups in R_3 and carboxylic acid groups in T, may take hemi-ketal (or hemi-acetal) or hydrated forms. For example, compounds

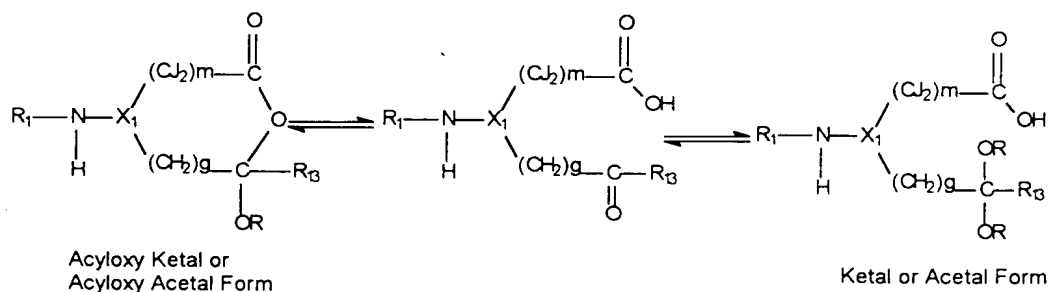
5

EQ1



Depending on the choice of solvent and other conditions known to the practitioner skilled in the art, compounds of this invention may also take acyloxy ketal, acyloxy acetal, ketal or acetal form:

10



In addition, it should be understood that the equilibrium forms of the compounds of this invention may include tautomeric forms. All such forms of these compounds are expressly included in the present

15

invention. It should be understood that the compounds of this invention may be modified by appropriate

- 287 -

functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion. In addition, the compounds may be altered to pro-drug form such that the desired compound is created in the body of the patient as the result of the action of metabolic or other biochemical processes on the pro-drug. Such pro-drug forms typically demonstrate little or no activity in *in vitro* assays. Some examples of pro-drug forms include ketal, acetal, oxime, imine, and hydrazone forms of compounds which contain ketone or aldehyde groups, especially where they occur in the R₃ group of the compounds of this invention. Other examples of pro-drug forms include the hemi-ketal, hemi-acetal, acyloxy ketal, acyloxy acetal, ketal, and acetal forms that are described in EQ1 and EQ2.

ICE and TX Cleave and Thereby Activate Pro-IGIF

The ICE protease was identified previously by virtue of its ability to process inactive pro-IL-1 β to mature active IL-1 β , a pro-inflammatory molecule, in vitro and in vivo. Here we show that ICE and its close homologue TX (Caspase-4, C. Faucheu et al., EMBO, 14, p. 1914 (1995)) can proteolytically cleave inactive pro-IGIF. This processing step is required to convert pro-IGIF to its active mature form, IGIF. Cleavage of pro-IGIF by ICE, and presumably by TX, also facilitates the export of IGIF out of cells.

- 288 -

We first used transient co-expression of plasmids transfected into Cos cells to determine whether any known members of the ICE/CED-3 protease family can process pro-IGIF to IGIF in cultured cells
5 (Example 23) (Fig. 1A).

Fig. 1A demonstrates that ICE cleaves pro-IGIF in Cos cells co-transfected with plasmids that express pro-IGIF in the presence of active ICE. Cos cells were transfected with an expression plasmid for
10 pro-IGIF alone (lane 2) or in combination with the indicated expression plasmids encoding wild type or inactive mutants of ICE/CED-3 family of proteases (lanes 3-12). Cell lysates were prepared and analyzed for the presence of IGIF protein by immunoblotting with
15 an anti-IGIF antiserum. Lane 1 contained lysates from mock transfected cells.

Co-expression of pro-IGIF with ICE or TX resulted in the cleavage of pro-IGIF into a polypeptide similar in size to the naturally-occurring 18-kDa
20 mature IGIF. This processing event is blocked by single point mutations that alter the catalytic cysteine residues and thus inactivate ICE and TX (Y. Gu et al., EMBO, 14, p. 1923 (1995)).

Co-expression with CPP32 (Caspase-3), a
25 protease involved in programmed cell death (T. Fernandes-Alnemri et al., J. Biol. Chem., 269, p. 30761 (1994); D. W. Nicholson et al., Nature, 376, p. 37 (1995)), resulted in the cleavage of pro-IGIF into a smaller polypeptide, while co-expression with CMH-1
30 (Caspase-7), a close homolog of CPP32 (J. A. Lippke et al., J. Biol. Chem., 271, p. 1825 (1996)), failed to cleave pro-IGIF to any significant extent. Thus, ICE and TX appear to be capable of cleaving pro-IGIF into a

- 289 -

polypeptide similar in size to the naturally-occurring 18-kDa IGIF.

We next examined the ability of these cysteine proteases to cleave pro-IGIF in vitro using a purified, recombinant (His)₆-tagged pro-IGIF as a substrate (**Example 23**).

Fig. 1B demonstrates that pro-IGIF is cleaved in vitro by ICE. Purified recombinant (His)₆-tagged pro-IGIF (2 µg) was incubated with the indicated cysteine protease in the presence or absence of ICE or CPP32 inhibitors as described in **Example 23**. The cleavage products were analyzed by SDS-PAGE and Coomassie Blue staining.

ICE cleaved the 24 kDa pro-IGIF into two polypeptides of approximately 18-kDa and 6-kDa. N-terminal amino acid sequencing of the ICE cleavage products indicated that the 18-kDa polypeptide contains the same N-terminal amino acid residues (Asn-Phe-Gly-Arg-Leu) as the naturally occurring IGIF. This shows that ICE cleaves pro-IGIF at the authentic processing site (Asp35-Asn36) (H. Okamura et al., Infection and Immunity, 63, p. 3966 (1995); H. Okamura et al., Nature, 378, p. 88 (1995)). N-terminal amino acid sequencing of the CPP32 cleavage products indicated that CPP32 cleaved pro-IGIF at Asp69-Ile70.

The cleavage by ICE of pro-IGIF is highly specific with a catalytic efficiency (k_{cat}/K_M) of $1.4 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ ($K_M = 0.6 \pm 0.1 \text{ µM}$; $k_{cat} = 8.6 \pm 0.3 \text{ s}^{-1}$) and is inhibited by specific ICE inhibitors (Ac-Tyr-Val-Ala-Asp-aldehyde) and Cbz-Val-Ala-Asp-[(2,6-dichlorobenzoyl)oxy]methylketone, (N.A. Thornberry et al., Nature, 356, p. 768 (1992); R. E. Dolle et al., J. Med. Chem., 37, p. 563 (1994)).

- 290 -

Fig. 1C demonstrates that ICE cleavage in vitro activates pro-IGIF. Uncleaved pro-IGIF, ICE- or CPP32-cleaved products of pro-IGIF, or recombinant mature IGIF (rIGIF) were each added to A.E7 cell
5 cultures to a final concentration of 12 ng/ml or 120 ng/ml (see, **Example 23**). Eighteen hours later, IFN- γ in the cultural medium was quantified by ELISA. While the uncleaved pro-IGIF had no detectable IFN- γ inducing activity, ICE-cleaved pro-IGIF was active in inducing
10 IFN- γ production in Th1 cells.

Like ICE, the ICE homolog TX also cleaved pro-IGIF into similarly sized polypeptides. However, its catalytic efficiency was about two orders of magnitude lower than that shown for ICE.

15 Consistent with the observations from the Cos cell experiments above, CPP32 cleaved pro-IGIF at a different site (Asp69-Ile70) and the resulting polypeptides had little IFN- γ inducing activity (**Fig. 1C**). CMH-1 and granzyme B each failed to cleave
20 pro-IGIF to any significant extent.

Together, these results demonstrate that, both in Cos cells and in vitro, ICE and TX are capable of processing the inactive pro-IGIF precursor at the authentic maturation site to generate a biologically
25 active IGIF molecule.

Processing of Pro-IGIF by ICE Facilitates Its Export

IGIF is produced by activated Kupffer cells and macrophages in vivo and is exported out of the cells upon stimulation by endotoxin (H. Okamura et al.,
30 Infection and Immunity, 63, p. 3966 (1995); H. Okamura et al., Nature, 378, p. 88 (1995)). We used the Cos cell co-expression system (**Example 23**) to examine

- 291 -

whether the intracellular cleavage of pro-IGIF by ICE would facilitate the export of mature IGIF from the cell. Such is the case for pro-IL-1 β when it is cleaved by ICE into active IL-1 β (N.A. Thornberry et al., Nature, 356, p. 768 (1992)).

In **Fig. 2A**, Cos cells transfected with an expression plasmid for pro-IGIF alone (lanes 2 and 6) or in combination with an expression plasmid encoding wild type (lanes 3 and 7) or inactive mutant ICE (lanes 4 and 8) were metabolically labeled with ³⁵S-methionine (see, **Example 24**). Cell lysates (left) and conditioned medium (right) were immunoprecipitated with an anti-IGIF antiserum. The immunoprecipitated proteins were analyzed by SDS-PAGE and fluorography (**Fig. 2A**).

An 18-kDa polypeptide corresponding in size to mature IGIF was detected in the conditioned medium of Cos cells co-expressing pro-IGIF and ICE, while Cos cells co-expressing pro-IGIF and an inactive ICE mutant (ICE-C285S), or pro-IGIF alone (-) exported only very low levels of pro-IGIF and no detectable mature IGIF. We estimate that about 10% of the mature IGIF was exported from co-transfected cells, while greater than 99% of pro-IGIF was retained within the cells.

We also measured the presence of IFN- γ inducing activity in cell lysates and in the conditioned medium of the above transfected cells (see, **Example 24**). IFN- γ inducing activity was detected in both cell lysates and the conditioned medium of Cos cells co-expressing pro-IGIF and ICE, but not in cells expressing either pro-IGIF or ICE alone (**Fig. 2B**).

These results indicate that ICE cleavage of pro-IGIF facilitates the export of mature, active IGIF from cells.

- 292 -

Pro-IGIF is a Physiological Substrate of ICE In Vivo

To study the role of ICE in the proteolytic activation and export of IGIF under physiological conditions, we examined the processing of pro-IGIF and export of mature IGIF from lipopolysaccharide (LPS)-activated Kupffer cells harvested from Propionibacterium acnes-elicited wild type and ICE deficient (ICE-/-) mice (**Example 25**).

As shown in **Fig. 3A**, Kupffer cells from ICE-/- mice are defective in the export of IGIF. Kupffer cell lysates of wild type and ICE-/- mice contained similar amounts of IGIF as determined by ELISA. IGIF, however, could be detected only in the conditioned medium of wild type but not of the ICE-/- cells. Thus, ICE-deficient (ICE-/-) mice synthesize pro-IGIF, but fail to export it as extracellular pro-or mature IGIF.

To determine whether ICE-deficient (ICE-/-) mice process intracellular pro-IGIF but fail to export IGIF, Kupffer cells from wild type and ICE-/- mice were metabolically labeled with ³⁵S-methionine and IGIF immunoprecipitation experiments were performed on cell lysates and conditioned media as described in **Example 25**. These experiments demonstrated that unprocessed pro-IGIF was present in both wild type and ICE-/- Kupffer cells. However, the 18-kDa mature IGIF was present only in the conditioned medium of wild type and not ICE-/- Kupffer cells (**Fig. 3B**). This shows that active ICE is required in cells for the export of processed IGIF out of the cell.

In addition, conditioned medium from wild type but not from ICE-/- Kupffer cells contained IFN- γ inducing activity that was not attributed to the action

- 293 -

of IL-12 because it was insensitive to a neutralizing anti-IL-12 antibody. The absence of IGIF in the conditioned medium of ICE-/- Kupffer cells is consistent with the finding in Cos cells that the processing of pro-IGIF by ICE is required for the export of active IGIF.

Figs. 3C and 3D show that, in vivo, ICE-/- mice have reduced serum levels of IGIF and IFN- γ , respectively. Wild type (ICE+/+) and ICE-/- mice (n=3) primed with heat-inactivated *P. acnes* were challenged with LPS (**Example 26**), and the levels of IGIF (**Fig. 3C**) and IFN- γ (**Fig. 3D**) in the sera of challenged mice were measured by ELISA three hours after LPS challenge (**Example 25**).

The sera of ICE-/- mice stimulated by *P. acnes* and LPS contained reduced levels of IGIF (**Fig. 3C**) and no detectable IFN- γ inducing activity in the presence of an anti-IL-12 antibody. The reduced serum levels of IGIF likely accounts for the significantly lower levels of IFN- γ in the sera of ICE-/- mice (**Fig. 3D**), because we have observed no significant difference in the production of IL-12 in ICE-/- mice under these conditions. Consistent with this interpretation is the finding that non-adherent splenocytes from wild type and ICE-/- mice produced similar amounts of IFN- γ when stimulated with recombinant active IGIF in vitro. Thus the impaired production of IFN- γ is not due to any apparent defect in the T cells of the ICE-/- mice.

Taken together, these results establish a critical role for ICE in processing the IGIF precursor and in the export of active IGIF both in vitro and in

- 294 -

vivo.

To examine in more detail the relationship between serum levels of IFN- γ and ICE activity in vivo, a time course after challenge of wild type and
5 ICE-deficient mice with LPS was performed (**Example 26**) (**Fig. 4**).

Fig. 4 shows a time course increase of serum IFN- γ in wild type mice, with sustained levels of ≥ 17 ng/ml occurring from 9-18 hrs after LPS challenge.
10 As predicted by the experiments discussed above, serum IFN- γ levels were significantly lower in ICE-/- mice, with a maximum of 2 ng/ml achieved over the same time period, which is approximately 15% of the level observed in wild type mice (**Fig. 4**).

15 Animals were also observed for clinical signs of sepsis and body temperature was measured at 4-hour intervals in wild type and ICE-/- mice challenged with 30 mg/kg or 100 mg/kg LPS (ICE-/-only). Results in **Fig. 4** show that wild type mice experienced a
20 significant decrease in body temperature (from 36°C to 26°C) within 12 hours of LPS challenge. Signs of clinical sepsis were evident and all animals expired within 24-28 hours.

In contrast, ICE-/- mice challenged with
25 30 mg/kg LPS experienced only a 3°-4°C decrease in body temperature with minimal signs of distress and with no observed lethality. ICE-/- mice challenged with 100 mg/kg LPS experienced clinical symptoms, a decrease in body temperature, and mortality similar to wild type
30 mice at the 30 mg/kg LPS dose.

- 295 -

The ICE Inhibitor Ac-YVAD-CHO is an Equipotent
Inhibitor of IL-1 β and IFN- γ Production

Since the processing and secretion of
biologically active IGIF is mediated by ICE, we
compared the activity of a reversible ICE inhibitor
(Ac-YVAD-CHO) on IL-1 β and IFN- γ production in a
peripheral blood mononuclear cell (PBMC) assay
(**Examples 27**).

Results in **Fig. 5** show a similar potency for
the ability of the Ac-YVAD-CHO ICE inhibitor to
decrease IL-1 β and IFN- γ production in human PBMCs,
with an IC₅₀ of 2.5 μ M for each. Similar results were
obtained in studies with wild type mouse splenocytes.

These findings provide additional evidence
that pro-IGIF is a physiological substrate for ICE and
suggest that ICE inhibitors will be useful tools for
controlling physiological levels of IGIF and IFN- γ .

In summary, we have found that ICE controls
IGIF and IFN- γ levels in vivo and in vitro and that ICE
inhibitors can decrease levels of IGIF and IFN- γ in
human cells. These results have been described in co-
pending United States Application Serial No.
08/712,878, the disclosure of which is herein
incorporated by reference.

Compositions and Methods

The pharmaceutical compositions and methods
of this invention will be useful for controlling IL-1,
IGIF and IFN- γ levels in vivo. The methods and
compositions of this invention will thus be useful for
treating or reducing the advancement, severity of
effects of IL-1, IGIF- and IFN- γ -mediated conditions.

- 296 -

The compounds of this invention are effective ligands for ICE. Accordingly, these compounds are capable of targeting and inhibiting events in IL-1-, apoptosis-, IGIF-, and IFN- γ -mediated diseases, and, thus, the ultimate activity of that protein in inflammatory diseases, autoimmune diseases, destructive bone, proliferative disorders, infectious diseases, and degenerative diseases. For example, the compounds of this invention inhibit the conversion of precursor IL-1 β to mature IL-1 β by inhibiting ICE. Because ICE is essential for the production of mature IL-1, inhibition of that enzyme effectively blocks initiation of IL-1-mediated physiological effects and symptoms, such as inflammation, by inhibiting the production of mature IL-1. Thus, by inhibiting IL-1 β precursor activity, the compounds of this invention effectively function as IL-1 inhibitors.

Similarly, compounds of this invention inhibit the conversion of precursor IGIF to mature IGIF. Thus, by inhibiting IGIF production, the compounds of this invention effectively function as inhibitors of IFN- γ production.

Accordingly, one embodiment of this invention provides a method for decreasing IGIF production in a subject comprising the step of administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of an ICE inhibitor and a pharmaceutically acceptable carrier.

Another embodiment of this invention provides a method for decreasing IFN- γ production in a subject comprising the step of administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of an ICE inhibitor and a

- 297 -

pharmaceutically acceptable carrier.

In another embodiment, the methods of this invention comprise the step of administering to a subject a pharmaceutical composition comprising an inhibitor of an ICE-related protease that is capable of cleaving pro-IGIF to active IGIF, and a pharmaceutically acceptable carrier. One such ICE-related protease is TX, as described above. This invention thus provides methods and pharmaceutical compositions for controlling IGIF and IFN- γ levels by administering a TX inhibitor.

Other ICE-related proteases capable of processing pro-IGIF into an active IGIF form may also be found. Thus it is envisioned that inhibitors of those enzymes may be identified by those of skill in the art and will also fall within the scope of this invention.

The compounds of this invention may be employed in a conventional manner for the treatment of diseases which are mediated by IL-1, apoptosis, IGIF or IFN- γ . Such methods of treatment, their dosage levels and requirements may be selected by those of ordinary skill in the art from available methods and techniques. For example, a compound of this invention may be combined with a pharmaceutically acceptable adjuvant for administration to a patient suffering from an IL-1-, apoptosis-, IGIF- or IFN- γ -mediated disease in a pharmaceutically acceptable manner and in an amount effective to lessen the severity of that disease.

Alternatively, the compounds of this invention may be used in compositions and methods for treating or protecting individuals against IL-1-, apoptosis-, IGIF- or IFN- γ -mediated diseases over

extended periods of time. The compounds may be employed in such compositions either alone or together with other compounds of this invention in a manner consistent with the conventional utilization of ICE inhibitors in pharmaceutical compositions. For example, a compound of this invention may be combined with pharmaceutically acceptable adjuvants conventionally employed in vaccines and administered in prophylactically effective amounts to protect individuals over an extended period of time against IL-1-, apoptosis-, IGIF- or IFN- γ - mediated diseases.

The compounds of this invention may also be co-administered with other ICE inhibitors to increase the effect of therapy or prophylaxis against various IL-1-, apoptosis, IGIF- or IFN- γ -mediated diseases.

In addition, the compounds of this invention may be used in combination either conventional anti-inflammatory agents or with matrix metalloprotease inhibitors, lipoxxygenase inhibitors and antagonists of cytokines other than IL-1 β .

The compounds of this invention can also be administered in combination with immunomodulators (e.g., bropirimine, anti-human alpha interferon antibody, IL-2, GM-CSF, methionine enkephalin, interferon alpha, diethyldithiocarbamate, tumor necrosis factor, naltrexone and rEPO) or with prostaglandins, to prevent or combat IL-1-mediated disease symptoms such as inflammation.

When the compounds of this invention are administered in combination therapies with other agents, they may be administered sequentially or concurrently to the patient. Alternatively, pharmaceutical or prophylactic compositions according

- 299 -

to this invention comprise a combination of an ICE inhibitor of this invention and another therapeutic or prophylactic agent.

Pharmaceutical compositions of this invention
5 comprise any of the compounds of the present invention, and pharmaceutically acceptable salts thereof, with any pharmaceutically acceptable carrier, adjuvant or vehicle. Pharmaceutically acceptable carriers,
10 adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as α -tocopherol
15 polyethyleneglycol 1000 succinate, or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine
20 sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers,
25 polyethylene glycol and wool fat. Cyclodextrins such as α -, β - and γ -cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2-and 3-hydroxypropyl- β -cyclodextrines, or
30 other solubilized derivatives may also be advantageously used to enhance delivery of compounds of this invention.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by

- 300 -

inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. We prefer oral administration. The pharmaceutical compositions of this invention may contain any
5 conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compounds or
10 its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

15 The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable
20 dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a
25 solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending
30 medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable

Sub
A3

- 301 -

Sub
A?

5

oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant such as Ph. Helv or a similar alcohol.

10

15

20

25

30

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical

- 302 -

composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention
5 include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream
10 containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The
15 pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-administered transdermal patches are also included in this invention.

20 The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline,
25 employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

30 Dosage levels of between about 0.01 and about 100 mg/kg body weight per day, preferably between about 1 and 50 mg/kg body weight per day of the active ingredient compound are useful in the prevention and treatment of IL-1-, apoptosis, IGIF and IFN- γ -mediated

- 303 -

diseases, including inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, degenerative diseases, necrotic diseases, osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, adult respiratory distress syndrome, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, graft vs. host disease, osteoporosis, multiple myeloma-related bone disorder, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma sepsis, septic shock, Shigellosis, Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular atrophy, multiple sclerosis, AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, and neurological damage due to stroke. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Preferably, such preparations contain from about 20% to about 80% active compound.

Upon improvement of a patient's condition, a

- 304 -

5 maintenance dose of a compound, composition or
combination of this invention may be administered, if
necessary. Subsequently, the dosage or frequency of
administration, or both, may be reduced, as a function
10 of the symptoms, to a level at which the improved
condition is retained when the symptoms have been
alleviated to the desired level, treatment should
cease. Patients may, however, require intermittent
treatment on a long-term basis upon any recurrence or
15 disease symptoms.

As the skilled artisan will appreciate, lower
or higher doses than those recited above may be
required. Specific dosage and treatment regimens for
any particular patient will depend upon a variety of
15 factors, including the activity of the specific
compound employed, the age, body weight, general health
status, sex, diet, time of administration, rate of
excretion, drug combination, the severity and course of
the disease, and the patient's disposition to the
20 disease and the judgment of the treating physician.

The IL-1 mediated diseases which may be
treated or prevented by the compounds of this invention
include, but are not limited to, inflammatory diseases,
autoimmune diseases, destructive bone disorders,
25 proliferative disorders, infectious diseases, and
degenerative diseases. The apoptosis-mediated diseases
which may be treated or prevented by the compounds of
this invention include degenerative diseases.

Inflammatory diseases which may be treated or
30 prevented include, but are not limited to
osteoarthritis, acute pancreatitis, chronic
pancreatitis, asthma, and adult respiratory distress
syndrome. Preferably the inflammatory disease is
osteoarthritis or acute pancreatitis.

- 305 -

Autoimmune diseases which may be treated or prevented include, but are not limited to, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, Crohn's disease, psoriasis, and graft vs. host disease. Preferably the autoimmune disease is rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, or psoriasis.

Destructive bone disorders which may be treated or prevented include, but are not limited to, osteoporosis and multiple myeloma-related bone disorder.

Proliferative diseases which may be treated or prevented include, but are not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, and multiple myeloma.

Infectious diseases which may be treated or prevented include, but are not limited to, sepsis, septic shock, and Shigellosis.

The IL-1-mediated degenerative or necrotic diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, Alzheimer's disease, Parkinson's disease, cerebral ischemia, and myocardial ischemia. Preferably, the degenerative disease is Alzheimer's disease.

The apoptosis-mediated degenerative diseases which may be treated or prevented by the compounds of

- 306 -

this invention include, but are not limited to, Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular atrophy, multiple sclerosis, AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, and neurological damage due to stroke.

The methods of this invention may be used for treating, or reducing the advancement, severity or effects of an IGIF-or IFN- γ -mediated inflammatory, autoimmune, infectious, proliferative, destructive bone, necrotic, and degenerative conditions, including diseases, disorders or effects, wherein the conditions are characterized by increased levels of IGIF or IFN- γ production.

Examples of such inflammatory conditions include, but are not limited to, osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, cerebral ischemia, myocardial ischemia and adult respiratory distress syndrome.

Preferably, the inflammatory condition is rheumatoid arthritis, ulcerative colitis, Crohn's disease, hepatitis and adult respiratory distress syndrome.

Examples of such infectious conditions include, but are not limited to, infectious hepatitis, sepsis, septic shock and Shigellosis.

Examples of such autoimmune conditions include, but are not limited to, glomerulonephritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), juvenile diabetes, autoimmune hemolytic anemia, autoimmune

- 307 -

neutropenia, thrombocytopenia, myasthenia gravis, multiple sclerosis, psoriasis, lichenplanus, graft vs. host disease, acute dermatomyositis, eczema, primary cirrhosis, hepatitis, uveitis, Behcet's disease, acute
5 dermatomyositis, atopic skin disease, pure red cell aplasia, aplastic anemia, amyotrophic lateral sclerosis and nephrotic syndrome.

Preferably the autoimmune condition is glomerulonephritis, insulin-dependent diabetes mellitus
10 (Type I), juvenile diabetes, psoriasis, graft vs. host disease, including transplant rejection, and hepatitis.

Examples of such destructive bone disorders include, but are not limited to, osteoporosis and multiple myeloma-related bone disorder.

15 Examples of such proliferative conditions include, but are not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, and multiple myeloma.

Examples of such neurodegenerative conditions
20 include, but are not limited to, Alzheimer's disease, Parkinson's disease and Huntington's disease.

Although this invention focuses on the use of the compounds disclosed herein for preventing and treating IL-1, apoptosis, IGF- and IFN- γ -mediated
25 diseases, the compounds of this invention can also be used as inhibitory agents for other cysteine proteases.

The compounds of this invention are also useful as commercial reagents which effectively bind to ICE or other cysteine proteases. As commercial
30 reagents, the compounds of this invention, and their derivatives, may be used to block proteolysis of a target peptide in biochemical or cellular assays for ICE and ICE homologs or may be derivatized to bind to a

- 308 -

stable resin as a tethered substrate for affinity chromatography applications. These and other uses which characterize commercial cystine protease inhibitors will be evident to those of ordinary skill in the art.

Process of Preparing N-Acylamino Compounds

The ICE inhibitors of this invention may be synthesized using conventional techniques. Advantageously, these compounds are conveniently synthesized from readily available starting materials.

The compounds of this invention are among the most readily synthesized ICE inhibitors known. Previously described ICE inhibitors often contain four or more chiral centers and numerous peptide linkages. The relative ease with which the compounds of this invention can be synthesized represents an advantage in the large scale production of these compounds.

For example, compounds of this invention may be prepared using the processes described herein. As can be appreciated by the skilled practitioner, these processes are not the only means by which the compounds described and claimed in this application may be synthesized. Further methods will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps described herein may be performed in an alternate sequence or order to give the desired compounds.

This invention also provides a preferred method for preparing the compounds of this invention. Accordingly, in another embodiment (M) is provided a process for preparing an N-acylamino compound comprising the steps of:

a) mixing a carboxylic acid with an N-

- 309 -

alloc-protected amino in the presence of an inert solvent, triphenylphosphine, a nucleophilic scavenger, and tetrakis-triphenyl phosphine palladium(0) at ambient temperature under an inert atmosphere; and

5 b) adding to the step a) mixture, HOBT and EDC; and optionally comprising the further step of:

 c) hydrolyzing the step b) mixture in the presence of a solution comprising an acid and H₂O, wherein the step b) mixture is optionally concentrated, prior to hydrolyzing.

10 Preferably, the inert solvent is CH₂Cl₂, DMF, or a mixture of CH₂Cl₂ and DMF.

 Preferably, the nucleophilic scavenger is dimesone, morpholine, trimethylsilyl dimethylamine, or dimethyl barbituric acid. More preferably, the nucleophilic scavenger is trimethylsilyl dimethylamine or dimethyl barbituric acid.

15 Preferably, the solution comprises trifluoroacetic acid in about 1-90% by weight. More preferably, the solution comprises trifluoroacetic acid in about 20-50% by weight.

 Alternatively, the solution comprises hydrochloric acid in about 0.1-30% by weight. More preferably, the solution comprises hydrochloric acid in about 0.1-30% by weight.

25 More preferably, in the above process, the inert solvent is CH₂Cl₂, DMF, or a mixture of CH₂Cl₂ and DMF and the nucleophilic scavenger is dimesone, morpholine, trimethylsilyl dimethylamine, or dimethyl barbituric acid.

30 Most preferably, in the above process the inert solvent is CH₂Cl₂, DMF, or a mixture of CH₂Cl₂ and DMF and the nucleophilic scavenger is trimethylsilyl dimethylamine or dimethyl barbituric acid.

- 310 -

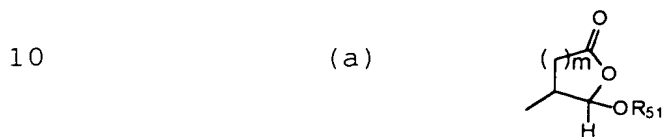
Preferably, the N-acyclamino compound is represented by formula (VIII):



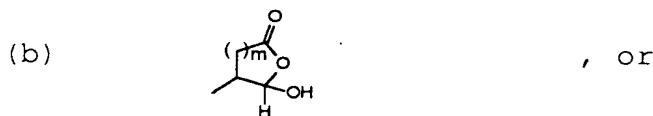
wherein:

R₁ is as defined above in embodiment (A);

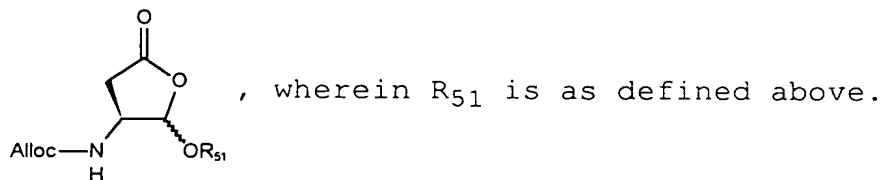
R₂ is:



wherein R₅₁ is as defined above in embodiment (B);



Preferably, the N-alloc-protected amine is:



20 In preferred processes, the substituents are as defined in embodiment (A).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R₁ is as defined

- 311 -

above in embodiment (B) and R_2 is as defined above in embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in
5 embodiment (B).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R_1 is as defined above in embodiment (C) and R_2 is as defined above in embodiment (M).

10 Preferably in these alternative processes, the substituents are as defined above in embodiment (C).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R_1 is as defined
15 above in embodiment (D) and R_2 is as defined above in embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in embodiment (D).

20 Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R_1 is as defined above in embodiment (E) and R_2 is as defined above in embodiment (M).

25 Preferably in these alternative processes, the substituents are as defined above in embodiment (E).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R_1 is as defined above in embodiment (F) and R_2 is as defined above in
30 embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in embodiment (F).

Alternatively, the N-acylamino compound is

- 312 -

represented by formula (VIII), wherein R_1 is as defined above in embodiment (G) and R_2 is as defined above in embodiment (G).

5 Preferably in these alternative processes, the substituents are as defined above in embodiment (G).

 Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R_1 is as defined above in embodiment (H) and R_2 is as defined above in
10 embodiment (M).

 Preferably in these alternative processes, the substituents are as defined above in embodiment (H).

 Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R_1 is as defined
15 above in embodiment (I) and R_2 is as defined above in embodiment (M).

 Preferably in these alternative processes, the substituents are as defined above in
20 embodiment (I).

 Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R_1 is as defined above in embodiment (J) and R_2 is as defined above in
embodiment (M).

25 Preferably in these alternative processes, the substituents are as defined above in embodiment (J).

 Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R_1 is as defined
30 above in embodiment (K) and R_2 is as defined above in embodiment (M).

 Preferably in these alternative processes, the substituents are as defined above in embodiment (K).

- 313 -

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R_1 is as defined above in embodiment (L) and R_2 is as defined above in embodiment (M).

5 Preferably in these alternative processes, the substituents are as defined above in embodiment (L).

In order that this invention be more fully understood, the following examples are set forth.

10 These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

- 314 -

Example 1

Inhibition of ICE

We obtained inhibition constants (K_i) and IC_{50} values for compounds of this invention using the three methods described below:

1. Enzyme assay with UV-visible substrate

This assay is run using an Succinyl-Tyr-Val-Ala-Asp-pNitroanilide substrate. Synthesis of analogous substrates is described by L. A. Reiter (Int. J. Peptide Protein Res. 43, 87-96 (1994)). The assay mixture contains:

65 μ l buffer (10mM Tris, 1 mM DTT, 0.1% CHAPS @pH 8.1)
10 μ l ICE (50 nM final concentration to give a rate of ~1mOD/min)
5 μ l DMSO/Inhibitor mixture
20 μ l 400 μ M Substrate (80 μ M final concentration)
100 μ l total reaction volume

The visible ICE assay is run in a 96-well microtiter plate. Buffer, ICE and DMSO (if inhibitor is present) are added to the wells in the order listed. The components are left to incubate at room temperature for 15 minutes starting at the time that all components are present in all wells. The microtiter plate reader is set to incubate at 37 °C. After the 15 minute incubation, substrate is added directly to the wells and the reaction is monitored by following the release of the chromophore (pNA) at 405 - 603 nm at 37 °C for 20 minutes. A linear fit of the data is performed and the rate is calculated in mOD/min. DMSO is only present during experiments involving inhibitors, buffer is used to make up the volume to 100 μ l in the other experiments.

- 315 -

2. Enzyme Assay with Fluorescent Substrate

This assay is run essentially according to Thornberry et al. (Nature 356: 768-774 (1992)), using substrate 17 referenced in that article. The substrate
5 is: Acetyl-Tyr-Val-Ala-Asp-amino-4-methylcoumarin (AMC). The following components are mixed:

65 μ l buffer (10mM Tris, 1mM DTT, 0.1% CHAPS @pH8.1)
10 μ l ICE (2 - 10 nM final concentration)
5 μ l DMSO/inhibitor solution
10 20 μ l 150 μ M Substrate (30 μ M final)
100 μ l total reaction volume

The assay is run in a 96 well microtiter plate. Buffer and ICE are added to the wells. The components are left to incubate at 37 °C for 15 minutes
15 in a temperature-controlled wellplate. After the 15 minute incubation, the reaction is started by adding substrate directly to the wells and the reaction is monitored @37 °C for 30 minutes by following the release of the AMC fluorophore using an excitation
20 wavelength for 380 nm and an emission wavelength of 460 nm. A linear fit of the data for each well is performed and a rate is determined in fluorescence units per second.

For determination of enzyme inhibition
25 constants (K_i) or the mode of inhibition (competitive, uncompetitive or noncompetitive), the rate data determined in the enzyme assays at varying inhibitor concentrations are computer-fit to standard enzyme kinetic equations (see I. H. Segel, Enzyme Kinetics,
30 Wiley-Interscience, 1975).

The determination of second order rate constants for irreversible inhibitors was performed by fitting the fluorescence vs time data to the progress equations of Morrison. Morrison, J.F., Mol. Cell.

- 316 -

Biophys., 2, pp. 347-368 (1985). Thornberry et al. have published a description of these methods for measurement of rate constants of irreversible inhibitors of ICE. Thornberry, N.A., et al.

5 Biochemistry, 33, pp. 3923-3940 (1994). For compounds where no prior complex formation can be observed kinetically, the second order rate constants (k_{inact}) are derived directly from the slope of the linear plots of k_{obs} vs. $[I]$. For compounds where prior complex

10 formation to the enzyme can be detected, the hyperbolic plots of k_{obs} vs. $[I]$ are fit to the equation for saturation kinetics to first generate K_i and k' . The second order rate constant k_{inact} is then given by k'/K_i .

15 3. PBMC Cell assay

IL-1 β Assay with a Mixed Population of Human
Peripheral Blood Mononuclear Cells (PBMC)
or Enriched Adherent Mononuclear Cells

Processing of pre-IL-1 β by ICE can be

20 measured in cell culture using a variety of cell sources. Human PBMC obtained from healthy donors provides a mixed population of lymphocyte subtypes and mononuclear cells that produce a spectrum of

interleukins and cytokines in response to many classes

25 of physiological stimulators. Adherent mononuclear cells from PBMC provides an enriched source of normal monocytes for selective studies of cytokine production by activated cells.

Experimental Procedure:

30 An initial dilution series of test compound in DMSO or ethanol is prepared, with a subsequent dilution into RPMI-10% FBS media (containing 2 mM L-glutamine, 10 mM HEPES, 50 U and 50 ug/ml pen/strep)

- 317 -

respectively to yield drugs at 4x the final test concentration containing 0.4% DMSO or 0.4% ethanol. The final concentration of DMSO is 0.1% for all drug dilutions. A concentration titration which brackets
5 the apparent K_i for a test compound determined in an ICE inhibition assay is generally used for the primary compound screen.

Generally 5-6 compound dilutions are tested and the cellular component of the assay is performed in
10 duplicate, with duplicate ELISA determinations on each cell culture supernatant.

PBMC Isolation and IL-1 Assay:

 Buffy coat cells isolated from one pint human blood (yielding 40-45 ml final volume plasma plus
15 cells) are diluted with media to 80 ml and LeukoPREP separation tubes (Becton Dickinson) are each overlaid with 10 ml of cell suspension. After 15 min centrifugation at 1500-1800 xg, the plasma/media layer is aspirated and then the mononuclear cell layer is
20 collected with a Pasteur pipette and transferred to a 15 ml conical centrifuge tube (Corning). Media is added to bring the volume to 15 ml, gently mix the cells by inversion and centrifuge at 300 xg for 15 min. Resuspend the PBMC pellet in a small volume of media,
25 count cells and adjust to 6×10^6 cells/ml.

 For the cellular assay, 1.0 ml of the cell suspension is added to each well of a 24-well flat bottom tissue culture plate (Corning), 0.5 ml test compound dilution and 0.5 ml LPS solution (Sigma
30 #L-3012; 20 ng/ml solution prepared in complete RPMI media; final LPS concentration 5 ng/ml). The 0.5 ml additions of test compound and LPS are usually sufficient to mix the contents of the wells. Three control mixtures are run per experiment, with either

- 318 -

LPS alone, solvent vehicle control, and/or additional media to adjust the final culture volume to 2.0 ml. The cell cultures are incubated for 16-18 hr at 37 °C in the presence of 5% CO₂.

5 At the end of the incubation period, cells are harvested and transferred to 15 ml conical centrifuge tubes. After centrifugation for 10 min at 200 xg, supernatants are harvested and transferred to 1.5 ml Eppendorf tubes. It may be noted that the cell
10 pellet may be utilized for a biochemical evaluation of pre-IL-1 β and/or mature IL-1 β content in cytosol extracts by western blotting or ELISA with pre-IL-1 β specific antisera.

Isolation of Adherent Mononuclear cells:

15 PBMC are isolated and prepared as described above. Media (1.0 ml) is first added to wells followed by 0.5 ml of the PBMC suspension. After a one hour incubation, plates are gently shaken and nonadherent cells aspirated from each well. Wells are then gently
20 washed three times with 1.0 ml of media and final resuspended in 1.0 ml media. The enrichment for adherent cells generally yields $2.5-3.0 \times 10^5$ cells per well. The addition of test compounds, LPS, cell incubation conditions and processing of supernatants
25 proceeds as described above.

ELISA:

 We have used Quantikine kits (R&D Systems) for measurement of mature IL-1 β . Assays are performed according to the manufacturer's directions. Mature
30 IL-1 β levels of about 1-3 ng/ml in both PBMC and adherent mononuclear cell positive controls are observed. ELISA assays are performed on 1:5, 1:10 and 1:20 dilutions of supernatants from LPS-positive

- 319 -

controls to select the optimal dilution for supernatants in the test panel.

The inhibitory potency of the compounds can be represented by an IC_{50} value, which is the
5 concentration of inhibitor at which 50% of mature IL-1 β is detected in the supernatant as compared to the positive controls.

The skilled practitioner realizes that values obtained in cell assays, such as those described
10 herein, can depend on multiple factors, such as cell type, cell source, growth conditions and the like.

Example 2

Pharmacokinetic Studies in the Mouse

15 Peptidyl ICE inhibitors are cleared rapidly with clearance rates greater than 100 μ /min/kg. Compounds with lower clearance rates have improved pharmacokinetic properties relative to peptidyl ICE inhibitors.

20 We obtained the rate of clearance in the mouse (μ /min/kg) for several compounds of this invention using the method described below:

Sample Preparation and Dosing

Compounds were dissolved in sterile TRIS
25 solution (0.02M or 0.05M) at a concentration of 2.5mg/ml. Where necessary to ensure a complete solution, the sample was first dissolved in a minimum of dimethylacetamide (maximum of 5% of total solution volume) then diluted with the TRIS solution.

30 The drug solution was administered to CD-1 mice (Charles River Laboratories - 26-31g) via the tail

- 320 -

vein at a dose volume of 10ml/kg giving a drug dose of 25mg/kg.

Mice were dosed in groups of 5 for each timepoint (generally from 2 minutes to 2 hours) then at the appropriate time the animals were anaesthetised with halothane and the blood collected into individual heparinized tubes by jugular severance. The blood samples were cooled to 0 °C then the plasma separated and stored at -20 °C until assayed.

10 Bioassay

Drug concentration in the plasma samples were determined by HPLC analysis with UV or MS (ESP) detection. Reverse phase chromatography was employed using a variety of bonded phases from C1 to C18 with eluents composed of aqueous buffer/acetonitrile mixtures run under isocratic conditions.

Quantitation was by external standard methods with calibration curves constructed by spiking plasma with drug solutions to give concentrations in the range of 0.5 to 50µg/ml.

Prior to analysis the plasma samples were deproteinated by the addition of acetonitrile, methanol, trichloroacetic acid or perchloric acid followed by centrifugation at 10,000g for 10 minutes. Sample volumes of 20µl to 50µl were injected for analysis.

Compound 214e

Dosing and sampling

The drug was dissolved in sterile 0.02M Tris to give a 2.5mg/ml solution which was administered to 11 groups of 5 male CD-1 mice via the tail vein at a dose of 25mg/kg. At each of the following timepoints: 2, 5, 10, 15, 20, 30, 45, 60, 90 and 120 minutes a

- 321 -

group of animals was anaesthetised and the blood collected into heparinized tubes. After separation the plasma was stored at -20 °C until assayed.

Assay

- 5 Aliquots of plasma (150µl) were treated with 5% perchloric acid (5µl) then mixed by vortexing and allowed to stand for 90 minutes prior to centrifugation. The resulting supernatant was separated and 20µl was injected for HPLC analysis.

10 HPLC Conditions

Column	100 x 4.6mm	Kromasil KR 100 5C4
Mobile Phase	0.1M Tris pH7.5	86%
	Acetonitrile	14%
Flowrate	1ml/min	
15 Detection	UV at 210nm	
Retention Time	3.4 mins	

The results of the analysis indicated a decrease in the mean plasma level of the drug from ~ 70µg/ml at 2 minutes to < 2µg/ml at 90 and 120 minutes.

20 Compound 217e

Dosing and sampling

- The drug was dissolved in sterile 0.02M Tris to give a 2.5mg/ml solution which was administered to 11 groups of 5 male CD-1 mice via the tail vein at a
- 25 dose of 25mg/kg. At each of the following timepoints: 2, 5, 10, 15, 20, 30, 45, 60, 90 and 120 minutes a group of animals was anaesthetised and the blood collected into heparinized tubes. After separation the plasma was stored at -20 °C until assayed.

- 322 -

Assay

Aliquots of plasma (100 μ l) were diluted with acetonitrile (100 μ l) then mixed by vortexing for 20 seconds before centrifugation for 10 minutes. The resulting supernatant was separated and 20 μ l was injected for HPLC analysis.

HPLC Conditions

Column 150 x 4.6mm Zorbax SBC8
Mobile Phase 0.05M Phosphate 72%
buffer pH 7.1
Acetonitrile 28%
Flowrate 1.4ml/min
Detection UV at 210nm
Retention Time 3.0 and 3.6 mins (diastereomers)

The results of the analysis indicated a decrease in mean plasma concentrations from ~ 55 μ g/ml at 2 minutes to < 0.2 μ g/ml at 60-120 minutes.

Example 3

Peptidyl ICE inhibitors are cleared rapidly with clearance rates greater than 80 ml/min/kg. Compounds with lower clearance rates have improved pharmacokinetic properties relative to peptidyl ICE inhibitors.

We obtained the rate of clearance in the rat (ml/min/kg) for several compounds of this invention using the method described below:

In vivo Rat Clearance Assay

Cannulations of the jugular and carotid vessels of rats under anesthesia were performed one day prior to the pharmacokinetic study. M.J. Free, R.A.

- 323 -

Jaffee; 'Cannulation techniques for the collection blood and other bodily fluids'; in: Animal Models; p. 480-495; N.J. Alexander, Ed.; Academic Press; (1978). Drug (10mg/mL) was administered via the
5 jugular vein in a vehicle usually consisting of: propylene glycol/saline, containing 100mM sodium bicarbonate in a 1:1 ratio. Animals were dosed with 10-20 mg drug/kg and blood samples were drawn at 0, 2, 5, 7, 10, 15, 20, 30, 60, and 90 minutes from an
10 indwelling carotid catheter. The blood was centrifuged to plasma and stored at -20 °C until analysis. Pharmacokinetic analysis of data was performed by non-linear regression using standard software such as RStrip (MicroMath Software, UT) and/or Pcnonlin (SCI
15 Software, NC) to obtain clearance values.

Analytical:

Rat plasma was extracted with an equal volume of acetonitrile (containing 0.1% TFA). Samples were then centrifuged at approximately 1,000 x g and the
20 supernatant analyzed by gradient HPLC. A typical assay procedure is described below.

200 µL of plasma was precipitated with 200 µL of 0.1% trifluoroacetic acid (TFA) in acetonitrile and 10 µL of a 50% aqueous zinc chloride solution, vortexed
25 then centrifuged at ~1000 x g and the supernatant collected and analyzed by HPLC.

HPLC procedure:

Column: Zorbax SB-CN (4.6 x 150 mm) (5µ particle size)
30 Column temperature: 50 °C
Flow rate: 1.0 mL/min
Injection volume: 75 µL.
Mobile phase: A=0.1% TFA in water and B=100% acetonitrile

- 324 -

Gradient employed: 100% A to 30% A in 15.5 min
0% A at 16 min
100% A at 19.2 min
Wavelength: 214 nm

5 A standard curve was run at 20, 10, 5, 2 and
1 µg/mL concentrations.

Example 4

Whole Blood Assay for IL-1 β Production

We obtained IC₅₀ values for several compounds
10 of this invention using the method described below:

Purpose:

Sub
AS
15 The whole blood assay is a simple method for
measuring the production of IL-1 β (or other cytokines)
and the activity of potential inhibitors. The
complexity of this assay system, with its full
complement of lymphoid and inflammatory cell types,
spectrum of plasma proteins and red blood cells is an
ideal in vitro representation of human in vivo
physiologic conditions.

20 Materials:

Pyrogen-free syringes (~ 30 cc)
Pyrogen-free sterile vacuum tubes containing
lyophilized Na₂EDTA (4.5 mg/10 ml tube)
Human whole blood sample (~ 30-50 cc)
25 1.5 ml eppendorf tubes
Test compound stock solutions (~ 25mM in DMSO or other
solvent)
Endotoxin-free sodium chloride solution (0.9%) and HBSS
Lipopolysaccharide (Sigma; Cat.# L-3012) stock solution
30 at 1mg/ml in HBSS

- 325 -

IL-1 β ELISA Kit (R & D Systems; Cat # DLB50)

TNF α ELISA Kit (R & D Systems; Cat # DTA50)

Water bath or incubator

Whole Blood Assay Experimental Procedure:

5 Set incubator or water bath at 30 °C.

Aliquot 0.25ml of blood into 1.5 ml eppendorf tubes.

Note: be sure to invert the whole blood sample tubes
after every two aliquots. Differences in replicates
may result if the cells sediment and are not uniformly
10 suspended. Use of a positive displacement pipette will
also minimize differences between replicate aliquots.

Prepare drug dilutions in sterile pyrogen-
free saline by serial dilution. A dilution series
which brackets the apparent K_i for a test compound
15 determined in an ICE inhibition assay is generally used
for the primary compound screen. For extremely
hydrophobic compounds, we have prepared compound
dilutions in fresh plasma obtained from the same blood
donor or in PBS-containing 5% DMSO to enhance
20 solubility.

Add 25 μ l test compound dilution or vehicle
control and gently mix the sample. Then add 5.0 μ l LPS
solution (250 ng/ml stocked prepared fresh: 5.0 ng/ml
final concentration LPS), and mix again. Incubate the
25 tubes at 30 °C in a water bath for 16-18 hr with
occasional mixing. Alternatively, the tubes can be
placed in a rotator set at 4 rpm for the same
incubation period. This assay should be set up in
duplicate or triplicate with the following controls:
30 negative control- no LPS; positive control- no test
inhibitor; vehicle control- the highest concentration
of DMSO or compound solvent used in the experiment.

- 326 -

Additional saline is added to all control tubes to normalize volumes for both control and experimental whole blood test samples

After the incubation period, whole blood
5 samples are centrifuged for 10 minutes at ~ 2000 rpm in the microfuge, plasma is transferred to a fresh microfuge tube and centrifuged at 1000 x g to pellet residual platelets if necessary. Plasma samples may be stored frozen at -70 °C prior to assay for cytokine
10 levels by ELISA.

ELISA:

We have used R & D Systems (614 McKinley Place N.E. Minneapolis, MN 55413) Quantikine kits for measurement of IL-1 β and TNF- α . The assays are
15 performed according to the manufacturer's directions. We have observed IL-1 β levels of ~ 1-5 ng/ml in positive controls among a range of individuals. A 1:200 dilution of plasma for all samples has been sufficient in our experiments for ELISA results to fall
20 on the linear range of the ELISA standard curves. It may be necessary to optimize standard dilutions if you observe differences in the whole blood assay. Nerad, J.L. et al., J. Leukocyte Biol., 52, pp. 687-692 (1992).

25

Example 5

Inhibition of ICE homologs

1. Isolation of ICE homologs

Expression of TX in insect cells using a baculovirus expression system. We have subcloned Tx cDNA (Faucheu
30 et al., supra 1995) into a modified pVL1393 transfer

- 327 -

vector, co-transfected the resultant plasmid
(pVL1393/TX) into insect cells with viral DNA and
identified the recombinant baculovirus. After the
generation of high titer recombinant virus stock, the
5 medium was examined for TX activity using the visible
ICE assay. Typically, infection of *Spodoptera*
frugiperda (Sf9) insect cells at an MOI of 5 with
recombinant virus stock resulted in a maximum
expression after 48 hours of 4.7µg/ml. ICE was used as
10 a standard in the assay.

Amino terminal T7 tagged versions of ICE or
TX were also expressed. Designed originally to assist
the identification and purification of the recombinant
proteins, the various constructs have also allowed
15 examination of different levels of expression and of
the relative levels of apoptosis experienced by the
different homologs. Apoptosis in the infected Sf9
cells (examined using a Trypan Blue exclusion assay)
was increased in the lines expressing ICE or TX
20 relative to cells infected with the viral DNA alone.

**Expression and purification of N-terminally (His)₆-
tagged CPP32 in *E. coli*.** A cDNA encoding a CPP32
(Fernandes-Alnemri et al, supra 1994) polypeptide
starting at Ser (29) was PCR amplified with primers
25 that add in frame XhoI sites to both the 5' and 3' ends
of the cDNA and the resulting XhoI fragment ligated
into a Xho I-cut pET-15b expression vector to create an
in frame fusion with (his)₆ tag at the n-terminus of
the fusion protein. The predicted recombinant protein
30 starts with the amino acid sequence of
MGSSHHHHHHSSGLVPRGSHMLE, where LVPRGS represents a
thrombin cleavage site, followed by CPP32 starting at

- 328 -

Ser (29). *E. coli* BL21(DE3) carrying the plasmid were grown to log phase at 30 °C and were then induced with 0.8 mM IPTG. Cells were harvested two hours after IPTG addition. Lysates were prepared and soluble proteins
5 were purified by Ni-agarose chromatography. All of the expressed CPP32 protein was in the processed form. N-terminal sequencing analysis indicated that the processing occurred at the authentic site between Asp (175) and Ser (176). Approximately 50 µg of CPP32
10 protein from 200 ml culture. As determined by active site titration, the purified proteins were fully active. The protease preparation were also very active in vitro in cleaving PARP as well as the synthetic DEVD-AMC substrate (Nicholson et al, supra 1995).

15 2. Inhibition of ICE homologs

The selectivity of a panel of reversible inhibitors for ICE homologs is depicted in Table 1. ICE enzyme assays were performed according to Wilson et al (supra 1994) using a YVAD-AMC substrate (Thornberry et al, supra
20 1992). Assay of TX activity was performed using the ICE substrate under identical conditions to ICE. Assay of CPP32 was performed using a DEVD-AMC substrate (Nicholson et al., supra 1995). In general, there is low selectivity between ICE and TX for a wide range of
25 scaffolds. None of the synthetic ICE compounds tested are effective inhibitors of CPP32. Assay of the reversible compounds at the highest concentration (1 µM) revealed no inhibition.

- 329 -

Table 1

Compound	K_i ICE (nM)	K_i TX (nM)	K_i CPP32 (nM)
214e	7.5	7.0 ± 1.1	> 1000
135a	90	55 ± 9	>1000
5 125b	60	57 ± 13	> 1000
137	40	40 ± 7	> 1000

Second-order rate constants for inactivation of ICE and ICE homologs with selected irreversible inhibitors are presented below (Table 2). The irreversible compounds studied are broad spectrum inhibitors of ICE and its homologs. Some selectivity, however, is observed with the irreversible compounds comparing inhibition of ICE and CPP32.

Table 2

Compound	k_{inact} (ICE) $M^{-1} s^{-1}$	k_{inact} (TX) $M^{-1} s^{-1}$	k_{inact} (CPP32) $M^{-1} s^{-1}$
138	120,000	150,000	550,000
217d	475,000	250,000	150,000
108a	100,000	25,000	nd

Example 6

20

Inhibition of apoptosis

Fas-Induced Apoptosis in U937 cells. Compounds were evaluated for their ability to block anti-Fas-induced apoptosis. In a preliminary experiment using RT-PCR, we detected mRNA encoding ICE, TX, ICH-1, CPP32 and

25

- 330 -

CMH-1 in unstimulated U937 cells. We used this cell line for apoptosis studies. U937 cells were seeded in culture at 1×10^5 cells/ml and grown to $\sim 5 \times 10^6$ cells/ml. For apoptosis experiments, 2×10^6 cells were plated in 24-well tissue culture plates in 1 ml RPMI-1640-10% FBS and stimulated with 100 ng/ml anti-Fas antigen antibody (Medical and Biological Laboratories, Ltd.). After a 24 hr incubation at 37 °C, the percentage of apoptotic cells was determined by FACS analysis using ApoTag reagents.

All compounds were tested initially at 20 μ M and titrations were performed with active compounds to determine IC₅₀ values. Inhibition of apoptosis (> 75% at 20 μ M) was observed for **108a**, **136**, and **138**. An IC₅₀ of 0.8 μ M was determined for **217e** compared to no inhibition of anti-Fas-induced apoptosis by **214e** at 20 μ M.

Example 7

In vivo acute assay for efficacy as anti-inflammatory agent

LPS-Induced IL-1 β Production.

Efficacy of **214e** and **217e** was evaluated in CD1 mice (n=6 per condition) challenged with LPS (20 mg/kg IP). The test compounds were prepared in olive oil:DMSO:ethanol (90:5:5) and administered by IP injection one hour after LPS. Blood was collected seven hours after LPS challenge. Serum IL-1 β levels were measure by ELISA. Results in **Fig. 6** show a dose dependent inhibition of IL-1 β secretion by **214e**, with

- 331 -

an ED₅₀ of approximately 15 mg/kg. Similar results were obtained in a second experiment. A significant inhibition of IL-1 β secretion was also observed in 217e treated mice (Fig. 7). However, a clear dose response was not apparent.

Compounds 214e and 217e (50 mg/kg) were also administered by oral gavage to assess absorption. Results in Fig. 8 show that 214e, but not 217e when administered orally inhibited IL-1 β secretion, suggesting potential for oral efficacy of ICE inhibitors as anti-inflammatory agents.

The efficacy of analogs of 214e were also evaluated in LPS challenged mice after IP administration (Fig. 9) and PO administration (Fig. 10).

Table 3 % Inhibition of IL- β production by analogs of 214e in LPS-challenged mice after PO and IP administration (50 mg/kg).

Table 3

Compound	PO% Inhibition	IP% Inhibition
214e	75	78
265	27	30
416	52	39
434	80	74
438	13	40
442	10	0
2002	-	78

- 332 -

Table 4

Comparison of 214e Prodrugs for
Efficacy in LPS Challenged Mice:
Time Course Inhibition of IL-1 β Production

Time of Compound Administration (relative to time of LPS challenge, PO, 50 mg/kg)					
5	Compound	-2 hr	-1 hr	0 hr	+1 hr
	214e	39*	-*	80*	55%
		43*	44*	48*	75*
		-*	-*	-*	11*
10	304a	30	33	68	47*
	2100e	49	54	94	37
	2100a	8	71	67	66
	213e	0	48	41	58
	302	0	27	21	89
	2100c	0	0	85	26
	2100d	42	35	52	40
15	2100b	0	0	47	26
	2001	~63	~62	~57	~54
		64*	62*	58*	55*

* Values obtained in subsequent assays

- 333 -

Example 8Measurement of blood levels of prodrugs of 214e.

Mice were administered a p.o. dose of compounds **302** and **304a** (50 mg/kg) prepared in 0.5 % carboxymethylcellulose. Blood samples were collected at 1 and 7 hours after dosing. Serum was extracted by precipitation with an equal volume of acetonitrile containing 2 % formic acid followed by centrifugation. The supernatant was analyzed by liquid chromatography-mass spectrometry (ESI-MS) with a detection level of 0.03 to 3 µg/ml. Compounds **302** and **304a** showed detectable blood levels when administered orally, **214e** itself shows no blood levels above 0.10 µg/mL when administered orally. Compounds **302** and **304a** are prodrugs of **214e** and are metabolized to **214e** in vivo (see Fig. 11).

Example 9

We obtained the following data (see Tables 5 and 6) for compounds of this invention using the methods described in Examples 1-8. The structures of the compounds of Example 9 are shown in Example 10-17.

Table 5

Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
47b	27	1800	<600	338	
47a	19	2600	5100	79	32
135a	90	2800	5000	>100	

- 334 -

	Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
	135b	320	1600	1700		
	125b	60	800	4500		
	108b	400	25000			>100
5	137	40	1700	14000		
	139	350	2000			
	213e	130	900	600 400*		
	214c	1200	5000			
	214e	7.5	1600	1300	23	12
	217c		1700	7000	70	
10	217e		175	2000	>50	
	220b	600	2125			
	223b	99	5000		>100	
	223e	1.6	3000	>20000	89	
	226e	15	1100	1800	109	
15	227e	7	234	550		
	230e		325	300	67	
	232e	1100	4500		22	26
	235e	510	4750		36	
	238e	500	4250			
20	246	12	950	10000	31	
	257	13	11000 6600*			
	265	47	4300	1400	23	20
	281	50	600 2500*			
	302	4500	>20000	>20000		
25	304a	200	1,400	2400 14000*		
	307a	55	14500	16000		
	307b	165		14000		
	404	2.9	1650 1800*	1100	64	24
	405	6.5	1700	2100		
30	406	4	1650	2300		
	407	0.4	540	1700		
	408	0.5	1100	1000	41	23

- 335 -

	Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
	409	3.7	2500			
	410	17	2000	2800	32	20
	411	0.9	540	1900		
	412	1.3	580 660*	700 1000*		25
5	413	750	6200			
	415	2.5	990 1000*	450 3500*	26	18
	416	12	1200	3400		47
	417	8	2000	6000	33	22
	418	2.2	1050 2200*	7800 1800*	13	5.9
10	419	280	>8000			
	420	1200	8000 >8000*			
	421	200	4300 4600*			
	422	50	2200	1200		
	423	10	2100 1800*	1500		45
15	424	45	2500	4000		
	425	0.8	650 700*	650		
	426	90	4500 2500*			
	427	180	4500			36
	428	280				
20	429	7000				
	430	60	>8000			
	431	8	>8000	8000		
	432	1.6	560	2000		
	433	2.9	1000 1100*	1100		
25	434	4.9	1600 1200*	1800 1300*		20
	435	8	4400			
	436	7.5	2700			
	437	12	1800	5000		

- 336 -

	Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
	438	28	1000	700 2900*		22
	439	3.7	2800	3200 3400*		
	440	2.3	5000	2000		
	441	1	2500	4500		
5	442	3.2	900	2000		54
	443	3.6	2800	1500		
	444	15	3500	3500		
	445	135		4000		
	446	62		3000		
10	447	5.8	2500	1500		
	448	130		4000		
	449	12	1500	3200 13000*		
	450	5	800	2200 1700*	18	12
	451	4	1800	1500 9000*		
15	452	4.5	600 800*	650 1600*		27.3
	453	0.65	1300	1900 1600*		
	454	45	2500			
	455	1.2	400	2800 2600*		54
	456	4.5	600 1300*	600 1400*		12.7
20	457	6.2	2000	3500		
	458	20	2900			
	459	5	1800			
	460	115	400	2400		
	461	47				
25	462	40				
	463	14	2400 2800*			
	464	2.5	1000	>1000 2500*		
	465	3	1000	800		

- 337 -

Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
466	0.8	1400	600		
467	11	1900			
468	4.5	850	2500		
470	5	500	360 500*		63
471	1	750	400		17
472	140				
473	1	1000	400 450*		
474	85				
475	5.5	690 650*	400 350*	31	21
476	7	1600	2500		
477	60				
478	380				
479	15	900	700 2400*		
480	25	2300			
481	1.2	390 930*	600 500*		34
482	<0.2	340	380 260*		
483	1.7	900	700		
484	2	1550 1400*	5000		15
485	2	900	900		
486	2.3	480 570*	500		37
487	2.4	650 950*	500 400*		20
488	1.5	940	750		
489	6	2250 1700*	15000		
490	4.3	980 1000*	700 1900*		
491	5	2500			
493	25	1200	800 850*		

- 338 -

	Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
	494	15	1350 1500*	7000		
	495	43				
	496	16	1550 1600*	6000		
	497	3.5	740	350 700*		
5	498	1.5	560	500 400*		
	499	3.5	1200 800*	9000		
	605a	90	2600	>20000		
	605b	45	10000		97	
	605c	615	4500		37	
10	605d	95	5100	16000 5100*	33	
	605e	29	2250	>10000		24
	605f	475	12500			
	605g	165	22500			
	605h	460	>25000			
15	605i	680	>20000			
	605j	110	8750		71	
	605m	650	20000			
	605n	12	2100	>20000	28	
	605o	72		18000		
20	605p	125	3200	>20000		
	605q	1000				
	605s	150	6000			
	605t	33				
	609a	114	>30000			
25	609b	27	>20000			
	619	300				
	620	35	1000	19000		
	621	7.2	1300	>20000		
	622	35	1300	>20000		
30	623	9				
	624	300				

- 339 -

	Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
	625	105				
	626	260				
	627	43	3250	8000		
	628	36	2750	>20000		
5	629	230				
	630	270				
	631	805				
	632	148				
	633	92	5750	20000		
10	634	1400				
	635	55	1900 3400*	4000		
	605v	1100	>30000			
	2201	9	2000 3700*	3500		60
	2100e	250	800	600		
15	2100a	100	1100	850		
	2002	4	810 860*	70 1400*		32
	2100d	>100000	>20000	>20000		
	2100c	7400	>20000	>20000		
	2100b	8000	>20000	>20000		
20	2001	135	1800	3500		
	1027	4000	>20000	>20000		60
	1015	40	2500	1700		23

Table 6

	Compound	Fluorescent Assay kinact M ⁻¹ s ⁻¹	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
25	108a	1x10 ⁵	17500			
	136	5.4x10 ⁵	870	2800	93	

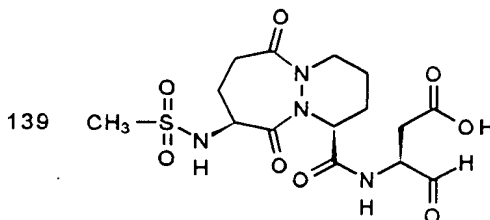
- 340 -

Compound	Fluorescent Assay kinact $M^{-1} s^{-1}$	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
138	1.2×10^5	900	2900	116	
217d	4.7×10^5	340	4000		
280	4×10^5	650	>1000		187
283	1×10^5	<200	450		104
284	3.5×10^5	470	550	77	100
285	4.3×10^5	810	1000	130	50

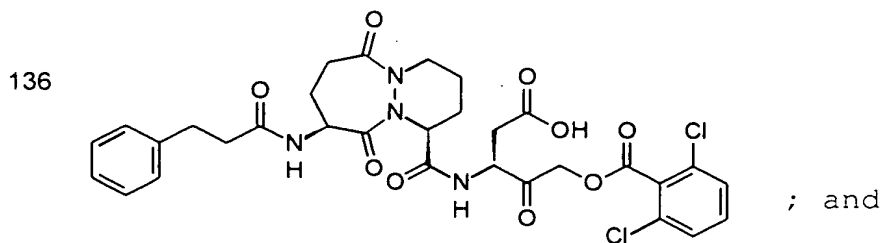
* Values obtained upon reassay.

Example 10

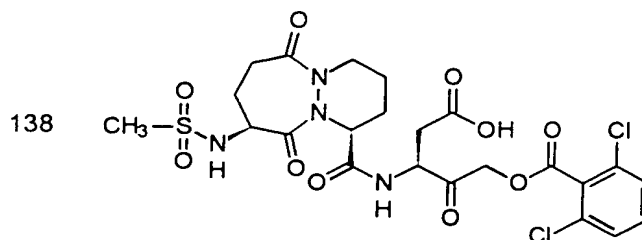
Compound 139 was synthesized by a method
10 similar to the method used to synthesize 47a.



Compounds 136 and 138 were synthesized by a
method similar to the method used to synthesize 57b.

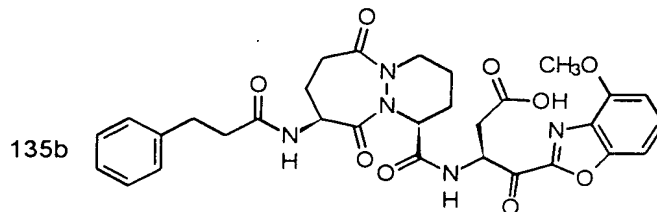
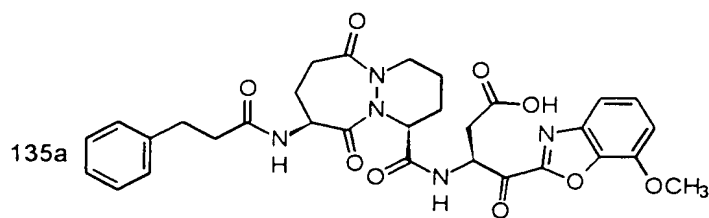


- 341 -

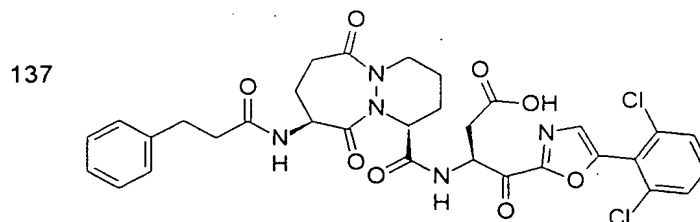


Compounds **135a**, **135b**, and **137** were synthesized by a method similar to the method used to synthesize **69a**.

5



; and



Compounds **813e**, **814c**, **814e**, **817c**, **817d**, **817e**, **820b**, **823b**, **823e**, **826e**, **827e**, **830e**, **832e**, **835e**, **838e**,
 10 **846**, **857**, **865**, **902**, **904a**, **907a**, **907b**, **1004-1013**, **1015-**

- 342 -

1045, 1046-1068, 1070-1091, and 1093-1099 were synthesized by methods similar to those used to synthesize compound **264** and the corresponding compounds in Examples 10 and 11.

5 Compounds **47a**, **47b**, **108a**, **108b**, **125b**, **213e**, **214c**, **217c**, **217d**, **217e**, **220b**, **223b**, **223e**, **226e**, **227e**, **230e**, **232e**, **235e**, **238e**, **246**, **257**, **264**, **265**, **280-287**, **302**, **304a**, **307a**, and **307b** were synthesized as described below.

10 H. N-(N-Acetyl-tyrosinyl-valinyl-pipecolyl)-3-amino-4-oxobutanoic acid.

Step A. N-(N-tert-Butoxycarbonylpipecolyl)-4-amino-5-benzyloxy-2-oxotetrahydrofuran.

15 Reaction of N-tert-butoxycarbonylpipecolic acid (460 mg, 2.0 mmol) and N-allyloxycarbonyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran (530 mg, 1.82 mmol) was carried out by a method analogous to that reported by Chapman (Bioorg. & Med. Chem. Lett. 2, pp. 613-618, (1992)) to give 654 mg of the title compound.

20 ¹H NMR (500 MHz, CDCl₃ (existing as rotamers)) δ 7.35 (m, 5H), 6.88 (br. s, 1H), 4.9-4.45(m, 4H), 3.95+ (br. m, 2H), 3.06 (m, 1H), 2.9 (m, 1H), 2.7 (br. m, 1H), 2.45 (m, 1H), 2.2 (m, 1H), 1.7-1.5 (m, 3H), 1.45 (two s, 9H).

25 Step B. N-Pipecolyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran.

N-(N-tert-Butoxycarbonylpipecolyl)-4-amino-5-benzyloxy-2-oxo-tetrahydrofuran (654 mg) was dissolved in 15 ml of 25% trifluoroacetic acid in dichloromethane

- 343 -

and stirred at room temperature. The mixture was concentrated to give a gummy residue. The residue was dissolved in dichloromethane and washed with 10% sodium bicarbonate. The organic layer was dried over
5 anhydrous sodium sulfate, filtered, and concentrated to give 422 mg of the title compound as a beige solid.

^1H NMR (500 MHz, CDCl_3) δ 7.38 (m, 5H), 7.15 (d, 1H), 5.55 (d, 1H), 4.95-4.8 (m, 1H), 4.78 (m, 1H), 4.65 (d, 1H), 4.45 (m, 1H), 3.2 (m, 0.5H), 3.05 (m,
10 0.5H), 2.95 (m, 0.5H), 2.85 (m, 0.5H), 2.65 (m, 1H), 2.55-2.38 (m, 1H), 1.95 (m, 1H), 1.8 (m, 1H), 1.6 (m, 2H), 1.38 (m, 2H).

Step C. N-(N-Acetyl-tyrosinyl-valinyl-
pipecolyl)-4-amino-5-benzyloxy-2-oxo-
15 tetrahydrofuran.

N-Acetyl-tyrosinyl-valine (464 mg, 1.44 mmol) and N-Pipecolyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran (412 mg, 1.3 mmol) were dissolved in 5 ml each of dimethylformamide and dichloromethane and
20 cooled to 0°C. To the cooled solution was added 1-hydroxybenzotriazole (HOBt; 210 mg, 1.56 mmol) followed by the addition of 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC; 326 mg, 1.7 mmol). After stirring for 18 hours, the mixture was
25 diluted with ethyl acetate and washed with water, 10% sodium hydrogen sulfate, 10% sodium bicarbonate, and water. The organic layer was concentrated to give a crude solid that was purified by flash chromatography (SiO_2) eluting with 94:6:1

- 344 -

(dichloromethane:isopropanol:pyridine) to give 370 mg of the title compound.

¹H NMR (500 MHz, CD₃OD (existing as diastereomers as well as rotamers)) δ 7.35 (m, 5H),
5 7.05 (m, 2H), 6.68 (m, 2H), 5.65 & 5.25 (m, 1H), 4.9-
3.95 (m, 8H), 3.4-2.6 (m, 4H), 2.5-2.1 (m, 1H), 1.98
(s, 1H), 1.9 (s, 1H), 1.85 (s, 1H), 1.8-1.6 (m, 2H),
1.55-1.3 (m, 4H), 0.95-0.85 (m, 6H).

Step D. N-(N-Acetyl-tyrosinyl-valinyl-
10 pipecolyl)-3-amino-4-oxobutanoic acid.

To a solution of 100 mg of N-(N-Acetyl-tyrosinyl-valinyl-pipecolyl)-4-amino-5-benzyloxy-2-oxotetrahydrofuran in 10 ml of methanol was added 60 mg of Pd(OH)₂ on carbon and the mixture placed under an
15 atmosphere of hydrogen via a balloon. The mixture was filtered through Celite and concentrated providing a white solid. This crude solid was dissolved in 2 ml of methanol and triturated with diethyl ether affording 26 mg of the title compound.

20 ¹H NMR (500 MHz, CD₃OD (existing as diastereomers as well as rotamers)) δ 7.1 (m, 2H), 6.7 (m, 2H), 5.2 (br. m, 1H), 4.8-3.6 (m, 6H), 3.2-2.5 (m, 4H), 2.5-2.1 (m, 1H), 1.95 (three s, 3H), 1.9-1.3 (m, 6H), 1.1-0.7 (m, 6H).

- 345 -

K. N-(N-Acetyl-tyrosinyl-valinyl-(4-benzyloxy)prolinyl)-3-amino-4-oxobutanoic acid.

5 Step A. N-(N-Allyloxycarbonyl-4-benzyloxyprolinyl)-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone.

The title compound was prepared by the reaction of N-allyloxycarbonyl-4-benzyloxyproline and 3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone (T.L. Graybill et. al., Abstracts of
10 papers, 206th National Meeting of the American Chemical Society, Abstract MEDI-235. Chicago, IL. (1993)) under similar peptide coupling conditions as reported above (compound H; Step C).

¹H NMR (500 MHz, CDCl₃) δ 9.05 (br. s, 1H),
15 7.85 (br. m, 1H), 7.4-7.2 (m, 5H), 7.15 (br. s, 1H),
6.55 (br. s, 1H), 5.9 (m, 1H), 5.1-4.9 (br. m, 2H),
4.65-4.4 (m, 4H), 4.2 (br. m, 1H), 3.75-3.5 (m, 2H),
2.75-2.55 (m, 2H), 2.5 (br. m, 1H), 2.25 (br. m, 1H)
1.4 (s, 9H).

Sub
A7
20 Step B. N-(N-Acetyl-tyrosinyl-valinyl-(4-benzyloxyprolinyl))-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone.

The title compound was prepared by reaction of N-acetyl-tyrosinyl-valine and N-(N-allyloxycarbonyl-
25 4-benzyloxyprolinyl)-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone by reaction conditions reported for compound H, step A.

Sub
A8
30 ¹H NMR (500MHz, CD₃OD) δ 7.35-7.2 (m, 6H), 7.0 (d, 2H), 6.65 (d, 2H), 4.85 (m, 1H), 4.6-4.45 (m, 4H),
4.3 (br. m, 1H), 4.15 (m, 1H), 3.7 (m, 1H), 2.95 (m,

- 346 -

Sub
A8

1H), 2.75-2.6 (m, 3H), 2.35 (m, 1H), 2.1 (m, 1H), 1.9 (s, 3H), 1.4 (s, 9H), 0.95 (d, 3H), 0.90 (s, 3H).

Sub
A9

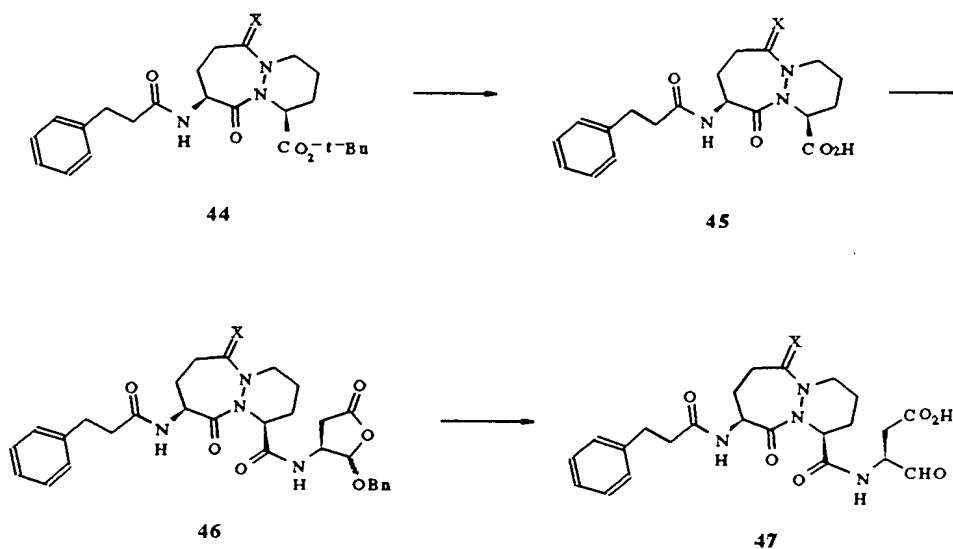
Step C. N-(N-Acetyl-tyrosinyl-valinyl-(4-benzyloxyprolinyl))-3-amino-4oxobutanoic acid.

5

N-(N-Acetyl-tyrosinyl-valinyl-(4-benzyloxyprolinyl))-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone (270 mg) was dissolved into 10 ml of 25% trifluoroacetic acid in dichloromethane and stirred at room temperature for 3 hours. The mixture was concentrated to give a solid residue. The residue was dissolved into a 10 ml mixture of methanol:acetic acid:37% formaldehyde (3:1:1) and stirred at room temperature for 1 hour. The mixture was concentrated and the resulting residue purified by flash chromatography (SiO₂) eluting with dichloromethane/methanol/formic acid (100:5:0.5) to give 37 mg of the title compound.

¹H NMR (500 MHz, CD₃OD (existing as a 1:1 mixture of diastereomers of the hemiacetal)) δ 7.4-7.25 (m, 5H), 7.0 (d, 2H), 6.65 (d, 2H), 4.65-4.05 (m, 7H), 3.75-3.4 (m, 2H), 3.05-2.3 (m, 5H), 2.2-1.95 (m, 2H), 1.90 (s, 3H), 1.0 (d, 3H), 0.95 (d, 3H).

- 347 -

(a) $X = O$ (b) $X = H_2$

(1*S*,9*S*) *t*-Butyl 6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6*H*-pyridazino[1,2-*a*]

- 5 [1,2]diazepine-1-carboxylate (44a). To a solution of (1*S*,9*S*)*t*-butyl 9-amino-6,10-dioxo-octahydro-6*H*-pyridazino [1,2-*a*][1,2]diazepine-1-carboxylate (690mg; 2.32mmol; GB 2128984) in dioxane (16ml) and water (4ml) at 0°C was added solid sodium bicarbonate (292mg; 3.48mmol) followed by dropwise addition of 3-phenylpropionyl chloride (470mg; 2.78mmol). The mixture was stirred at room temperature for 2h then more sodium bicarbonate (200mg; 2.38mmol) and 3-phenylpropionyl chloride (100mg; 0.6mmol) were added.
- 15 The mixture was stirred for a further 2h at room temperature, diluted with ethyl acetate (50ml), washed with saturated sodium bicarbonate (2 x 25ml) then dried (MgSO₄) and concentrated. The residue was purified by flash chromatography (0-50% ethyl acetate/chloroform)

- 348 -

and finally crystallized by trituration with ether to afford 860mg (86%) of a white solid: mp. 137-138°C; $[\alpha]_D^{23}$ -95.1° (c 0.549, CH₂Cl₂); IR (KBr) 3327, 1736, 1677, 1664, 1536, 1422, 1156; ¹H NMR (CDCl₃) δ 7.24

5 (5H, m), 6.50 (1H, d, J=7.5), 5.24 (1H, m), 4.90 (1H, m), 4.60 (1H, m), 3.44 (1H, m), 2.93 (2H, m), 2.84 (1H, m), 2.64 (1H, m), 2.54 (2H, m), 2.26 (2H, m), 1.70 (4H, m), 1.70 (9H, s). MS(FAB, m/z): 430 (M⁺ + 1), 374, 242, 105, 91.

10 (1S,9S) t-Butyl octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxylate (44b), was prepared from (1S,9S) t-butyl 9-amino-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (Attwood
15 et al., J. Chem. Soc. Perkin 1, pp. 1011-19 (1986)) as for 44a, to afford 810mg (81%) of a colorless oil:
 $[\alpha]_D^{23}$ - 33.5° (c 0.545, CH₂Cl₂); IR (film) 3334, 2935, 1737, 1728, 1659, 1642; ¹H NMR (CDCl₃) δ 7.24 (5H, m), 6.75 (1H, d, J=6.7), 5.27 (1H, m), 4.92 (1H, m), 3.39
20 (1H, m), 3.03 (4H, m), 2.55 (3H, m), 2.33 (1H, m), 2.17 (1H, m), 1.80 (5H, m), 1.47 (9H, s), 1.39 (1H, m).
MS(FAB, m/z): 416 (M⁺ + 1), 360, 211, 143, 97.

(1S,9S) 6,10-Dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid (45a). To a solution
25 of (1S,9S) t-butyl 6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (44a) (800mg; 1.863mmol) in dry dichloromethane (5ml) at 0°C was added
30 trifluoroacetic acid (5ml). The solution was stirred at room temperature for 3h then concentrated. Dry

- 349 -

ether (10ml) was added to the residue then removed under vacuum. This process was repeated three times to afford a crystalline solid. The solid was triturated with ether and filtered to afford 590mg (85%) of a
 5 white crystalline solid: mp. 196-197.5°C; $[\alpha]_D^{23}$ -129.5° (c 0.2, CH₃OH); IR (KBr) 3237, 1729, 1688, 1660, 1633, 1574, 1432, 1285, 1205; ¹H NMR (CD₃OD) δ 8.28 (1H, d, J=7.4), 7.22 (5H, m), 5.32 (1H, dd, J=5.9, 2.9), 4.75 (1H, m), 4.51 (1H, m), 3.50 (1H, m), 3.01 (1H, m), 2.91
 10 (2H, m), 2.55 (2H, m), 2.29 (3H, m), 1.95 (2H, m), 1.71 (2H, m). Anal. Calcd for C₁₉H₂₃N₃O₅: C, 61.12; H, 6.21; N, 11.25. Found: C, 60.80; H, 6.28; N, 10.97. MS(FAB, m/z) 374 (M⁺ + 1), 242, 105, 91.

(1*S*,9*S*) Octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-
 15 pyridazino[1,2-a]-[1,2]diazepine-1-carboxylic acid (45b), was prepared from (1*S*,9*S*) t-butyl octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (44b) by the method described for compound 45a to afford 657mg
 20 (96%) of 45b as a crystalline solid: mp. 198-202°C; $[\alpha]_D^{23}$ -86.2° (c 0.5, CH₃OH); IR (KBr) 3294, 2939, 1729, 1645, 1620, 1574, 1453, 1214; ¹H NMR (CD₃OD) δ 7.92 (1H, d, J=7.9), 7.20 (5H, m), 5.29 (1H, m), 4.90 (1H, m), 3.47 (1H, m), 3.08 (2H, m), 2.90 (2H, m), 2.55 (3H, m), 2.36 (1H, m), 1.81 (5H, m), 1.43 (2H, m). MS(FAB,
 25 m/z) 360 (M⁺ +1), 211,143,91.

[3*S*,2*R*,*S*, (1*S*,9*S*)] N-(2-Benzylloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (46a).
 30 To a solution of (1*S*,9*S*) 6,10-dioxo-octahydro-9-(3-phenyl-propionylamino)-6H-pyridazino[1,2-a]

- 350 -

[1,2]diazepine-1-carboxylic acid (**45a**) (662mg; 1.773mmol) in dry dichloromethane (9ml) and dry dimethyl formamide (3ml) at room temperature was added bis(triphenylphosphine)palladium chloride (30mg) and

5 (3*S*,2*R*,*S*)-3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran (Chapman, Bioorg. Med. Chem. Lett., 2, pp. 613-18 (1992)) (568mg; 1.95mmol) followed by dropwise addition of tri-*n*-butyltin hydride (1.19g; 4.09mmol). 1-Hydroxy-benzotriazole (479mg; 3.546mmol)

10 was added to the mixture and the mixture was cooled to 0°C before addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (408mg; 2.128mmol). The mixture was stirred at room temperature for 3.25h then diluted with ethyl acetate (50ml), washed twice

15 with dilute hydrochloric acid (20ml), twice with saturated sodium bicarbonate (20ml), once with brine then dried (MgSO₄) and concentrated. The resulting oil was purified by flash chromatography (0-100% ethyl acetate/chloroform) to afford 810mg (81%) of **46a** as a

20 mixture of anomers: mp. 92-94°C; IR (KBr) 3311, 1791, 1659, 1651, 1536; ¹H NMR(CDCl₃) δ 7.49, 6.56 (1H, 2d, *J*=6.7, 7.8), 7.29 (10H, m), 6.37, 6.18 (1H, 2d, *J*=7.7, 7.6), 5.56, 5.34 (1H, d, s, *J*=5.2), 5.08-4.47 (6H), 3.18-2.80 (5H), 2.62-2.28 (5H), 2.04-1.53 (5H).

25 MS(FAB, *m/z*), 563 (*M*⁺ + 1), 328, 149, 91.

[3*S*,2*R*,*S*,(1*S*,9*S*)] *N*-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-*a*]

[1,2]diazepine-1-carboxamide (**46b**), was prepared from

30 **45b** by the method described for **46a** to yield 790mg (96%) of a glass: m.p. 58-60°C; IR (KBr) 3316, 2940, 1793, 1678, 1641, 1523, 1453, 1120; ¹H NMR (CDCl₃) δ

- 351 -

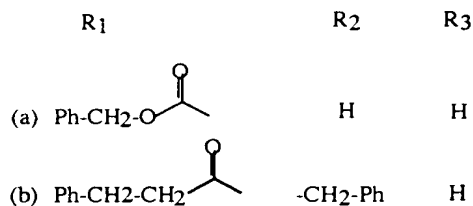
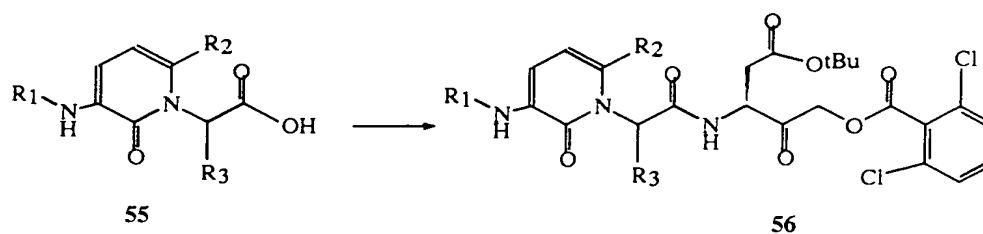
7.28 (10H, m), 6.52, 6.42 (1H, 2d, $J=7.2$, 7.1), 5.53, 5.44 (1H, d, s, $J=5.2$), 5.35 (1H, m), 4.6-4.9, 4.34 (4H, m), 3.1-2.8 (6H, m), 2.6-2.1 (7H), 1.95-1.05 (5H). MS (FAB, m/z), 549 ($M^+ + 1$), 400, 310, 279, 91.

- 5 [3*S*(1*S*,9*S*)] 3-(6,10-Dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (47a).
A mixture of [3*S*, 2*R*,*S*, (1*S*,9*S*)] N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (46a) (205mg; 0.364mmol), 10% palladium on carbon (200mg) and methanol (20ml) was stirred under hydrogen at atmospheric pressure for 5h. The mixture was filtered then concentrated to yield
15 154mg (90%) of a glass: mp. 116-118°C; $[\alpha]_D^{23}$ -140° (c 0.1, CH₃OH); IR (KBr) 3323 (br), 1783, 1731, 1658, 1539, 1455, 1425; ¹H NMR (CD₃OD) δ 7.21 (5H, m), 5.17 (1H, m), 4.73 (1H, m), 4.50 (2H, m), 4.23 (1H, m), 3.38 (1H, m), 3.06 (1H, m), 2.91 (2H, m), 2.73-2.18 (6H, m) and 2.01-1.59 (5H, m). Anal. Calcd for C₂₃H₂₇N₄O₇ + H₂O : C, 56.32; H, 6.16; N, 11.42. Found: C, 56.29; H, 6.11; N, 11.25. MS (FAB, m/z) 473 ($M^+ + 1$), 176, 149, 105, 91.

- [3*S*(1*S*,9*S*)] 3-(Octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (47b),
25 was prepared from 46b by the method described for 47a. The residue was purified by flash chromatography (0-10% methanol/chloroform) to afford 65mg (52%) of a glass;
30 m.p. 87-90°C; $[\alpha]_D^{23}$ -167.0° (c 0.1, methanol); IR (KBr) 3329, 2936, 1786, 1727, 1637; ¹H NMR (CD₃OD) δ

- 352 -

7.23 (5H, m), 5.29 (1H, m), 4.83 (1H, m), 4.59 (1H, d, $J=3.6$), 4.29 (1H, m), 3.3-3.0 (3H, m), 2.91 (2H, m), 2.70-2.34 (5H, m), 2.19 (2H, m), 1.75 (4H, m), 1.36 (2H, m). Anal. Calcd for $C_{23}H_{30}N_4O_6 + 0.5H_2O$: C, 59.09; H, 6.68; N, 11.98. Found: C, 58.97; 6.68; N, 11.73. MS (FAB, m/z) 459 ($M^+ + 1$), 310, 149, 105, 91.



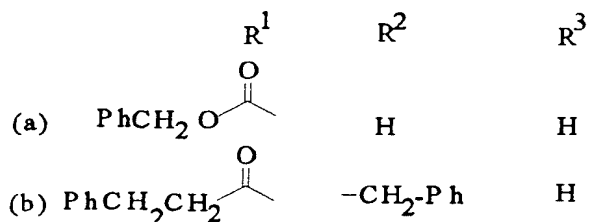
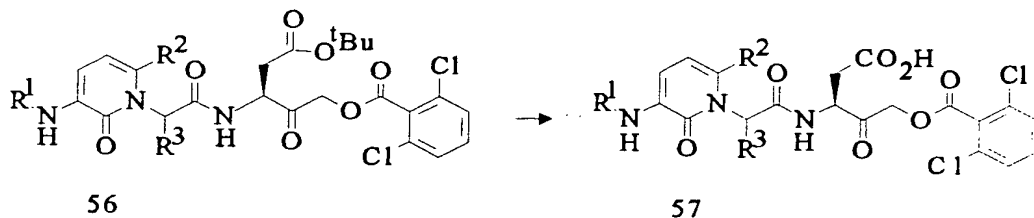
t-Butyl N-2-(3-benzyloxycarbonylamino-1,2-dihydro-2-oxo-1-pyridyl)acetyl-3-amino-5-(2,6-dichlorobenzoyloxy)-4-oxo-pentanoate (56a). The acetic acid (55a) (WO 93 21213) in THF (2ml) was stirred at room temperature and treated with 1-hydroxybenzotriazole (60mg, 0.448mmol) and dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (47mg, 0.246mmol). After 5 mins water (2 drops) was added and stirring continued for 20 minutes. Bis(triphenylphosphine) palladium II chloride (6mg) was added followed by a solution of t-butyl 3-(allyloxycarbonylamino)-4-oxo-5-(2,6-dichlorobenzoyl-oxy)pentanoate (WO 93 16710) (103mg, 0.224mmol) in THF (1ml). Tributyltin hydride

- 353 -

(0.09ml, 0.336mmol) was added dropwise over 1 hour at room temperature. The mixture was stirred for a further 3 hours and poured onto ethyl acetate, washed with 1M HCl, aqueous NaHCO₃, brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was triturated with pentane and the supernatant discarded. The remaining solid was purified by flash chromatography (50% ethyl acetate/hexane) to afford the title compound 92mg (63%) as a colorless oil: $[\alpha]_D^{26} -29.6^\circ$ (c 1.1, CH₂Cl₂); IR (film) 3377, 3365, 3332, 3312, 1733, 1691, 1650, 1599, 1515, 1366, 1261, 1153, 1068, 747; ¹H NMR (CDCl₃) δ 8.09 (1H, d, *J* = 6.8), 7.84 (1H, s), 7.58 (1H, d, *J* = 8.3), 7.33 (8H, m), 7.02 (1H, dd, *J* = 6.9, 1.7), 6.33 (1H, t, *J* = 7.2), 5.20 (2H, s), 5.12 (2H, m), 4.89 (1H, dt), 4.65 (2H, m), 2.80 (2H, m), 1.38 (9H, s).

t-Butyl N-2-(6-benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl)acetyl-3-amino-5-(2,6-dichlorobenzyloxy)-4-oxo-pentanoate (56b), was prepared by the method described for (56a) which afforded the title compound (66%) as a colorless oil: IR (film) 3364, 3313, 1738, 1688, 1648, 1600, 1566, 1514, 1433, 1369, 1254, 1152; ¹H NMR (CDCl₃) δ 8.40 (1H, d, *J* 7.6), 8.30 (1H, s), 7.28 (13H, m), 6.20 (1H, d, *J* = 7.6), 5.12 (2H, q), 4.86 (1H, m), 4.65 (2H, q), 4.06 (2H, s), 3.07-2.61 (6H, m), 1.39 (9H, s).

- 354 -



N-2(3-Benzoyloxycarbonylamino-1,2-dihydro-2-oxo-1-pyridyl)acetyl-3-amino-5-(2,6-dichlorobenzoyloxy)-4-oxo-pentanoic acid (57a; Q). The ester 56a (210mg, 0.356mmol) in dichloromethane (0.5ml) was cooled to 0°C and treated with trifluoroacetic acid (0.5ml), stirred and warmed to 20°C over 30 minutes. The solution was evaporated to dryness under reduced pressure, redissolved in dichloromethane and concentrated (x3). The residue was triturated with ethyl acetate and diluted with ether to afford the title compound 162mg (85%) as a colorless solid: m.p. 165-8°C (decomposition); $[\alpha]_D^{23}$ -38.8° (c 0.1, CH₃OH); IR (KBr) 3332, 3275, 1723, 1658, 1649, 1597, 1581, 1562, 1526, 1432, 1385, 1258, 1218, 1206; ¹H NMR (d₆-DMSO) δ 8.96 (1H, d, J = 7.3), 8.34 (1H, s), 7.85 (1H, dd, J = 7.3), 7.58 (3H, m), 7.35 (5H, m), 6.29 (1H, t, J = 7.3), 5.26 (2H, m), 5.15 (2H, s), 4.69 (3H, m), 2.75 (2H, m). Anal. Calcd. C₂₇H₂₃N₃O₉Cl₂: C, 53.66; H, 3.84; N, 6.95. Found: C, 53.36; H, 3.90; N, 6.81. M.S. (+ FAB); 604 (M⁺ + 1), 285, 241, 195, 173, 149, 91.

- 355 -

N-2-(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl) amino-1-pyridyl)acetyl-3-amino-5-(2,6-dichloro-benzoyloxy)-4-oxo-pentanoic acid (57b; P), was prepared by the method described for 57a which afforded the

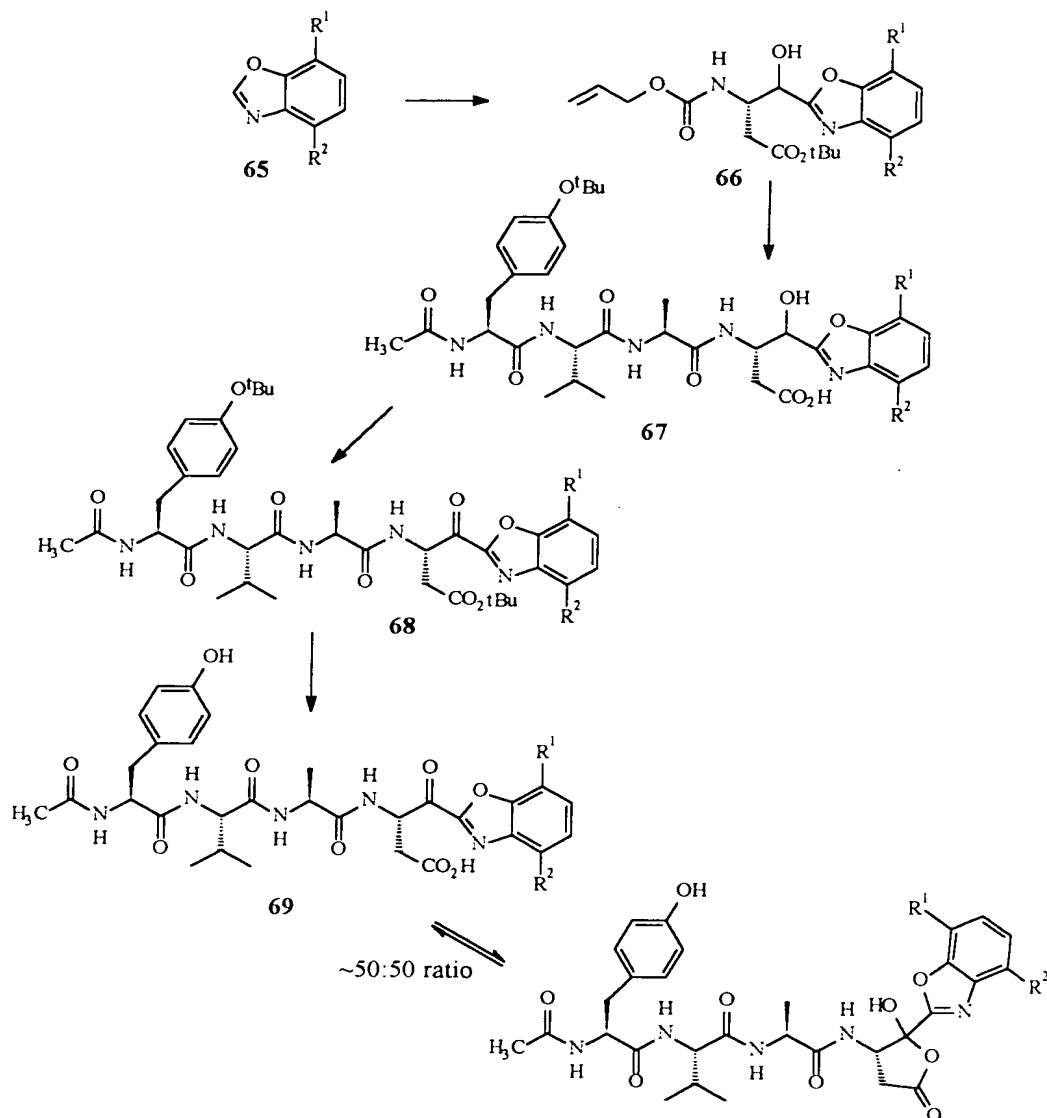
5 title compound (78%) as colorless crystals: m.p. 116-120°C (decomposition); $[\alpha]_D^{26} -41.1^\circ$ (c 0.1, CH₃OH); IR (KBr) 3299, 1739, 1715, 1689, 1666, 1645, 1598, 1563, 1518, 1432, 1209, 1151; ¹H NMR (d₆-DMSO) δ 9.24 (1H, s), 8.88 (1H, d, $J = 7.6$), 8.18 (1H, d, $J = 7.7$), 7.60

10 (3H, m), 7.26 (10H, m), 6.06 (1H, d, $J = 7.7$), 5.23 (2H, ABq), 4.69 (3H, m), 3.93 (2H, s), 2.78 (6H, m).

Anal. Calcd. for C₃₅H₃₁N₃O₈Cl₂ · H₂O: C, 59.16; H, 4.68; N, 5.91. Found: C, 59.38; H, 4.53; N, 5.84. M.S. (+ FAB); 694, (Cl=35, 37), (M⁺ + 1); 692 (Cl=35, 35), (M⁺

15 + 1).

- 356 -

(a) $R^1 = \text{OCH}_3$, $R^2 = \text{H}$ (b) $R^1 = \text{H}$, $R^2 = \text{OCH}_3$

7-Methoxybenzoxazole (65a). A mixture of 2-nitro-6-methoxyphenol (2.62g, 15.5mmol) (EP 333176) and 10% Palladium on carbon (130mg) in ethanol (50.0ml) was stirred under an atmosphere of H_2 for 75min. The

- 357 -

mixture was filtered through Celite® then immediately treated with *p*-toluenesulphonic acid (32.0mg) and triethylorthoformate (6.45ml, 38.8mmol) then heated under reflux under an atmosphere of N₂. After 20h *p*-toluenesulphonic acid (30.0mg) and triethylorthoformate (6.45ml, 38.8mmol) were added. After a total of 44h heating, the reaction was allowed to cool and reduced *in vacuo*. The resulting residue was purified by flash chromatography (25:75 ethyl acetate/hexane) to give 1.97g (85%) of the title compound as a yellow solid: m.p. 28-31°C; IR (film) 1629, 1497, 1434, 1285, 1097; ¹H NMR (CDCl₃) δ 8.09 (1H, s), 7.40 (1H, d, *J* = 8.0), 7.28 (1H, t, *J* = 8.0), 6.89 (1H, d, *J* = 8.0), 4.02 (3H, s); ¹³C NMR (CDCl₃) δ 152.84, 145.82, 142.50, 139.99, 125.75, 113.42, 108.80, 56.97. Anal. Calcd. for C₈H₇N₁O₂ · 0.1H₂O: C, 63.65; H, 4.81; N, 9.29. Found: C, 63.43, H, 4.88, N, 9.05. M.S. (+ FAB); 150 (M⁺ + 1).

4-Methoxybenzoxazole (65b). To a suspension of 4-hydroxybenzoxazole (2.00g, 14.8mmol) (Musser et al., J. Med. Chem., 30, pp. 62-67 (1987)) in acetone (80.0ml) was added dried K₂CO₃ (2.25g, 16.3mmol) followed by iodomethane (1.38ml, 22.2mmol). The reaction was heated under reflux under N₂ for 4.5h, then filtered and reduced *in vacuo* to afford the crude product. The resulting residue was purified by flash chromatography (25:75 ethyl acetate/hexane) to give 2.0g (91%) of the title compound as a white crystalline solid: m.p. 72-74°C; IR (KBr) 3089, 1619, 1610, 1503, 1496, 1322, 1275, 1090, 1071, 780, 741; ¹H NMR (CDCl₃) δ 8.02 (1H, s), 7.32 (1H, t, *J* = 8.0), 7.18 (1H, d, *J* = 8.0), 6.81 (1H, d, *J* = 8.0), 4.04 (3H, s). Anal. Calcd. for

- 358 -

$C_8H_7NO_2$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.40; H, 4.84; N, 9.31; m/z (EI) 149 ($M^+ + 1$, 100%).

(3*S*, 4*R*,*S*) t-Butyl N-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(2-(7-methoxybenzoxazolyl))butanoate (66a).

- 5 To a stirred solution of 7-methoxybenzoxazole **65a** (548.6mg, 3.68mmol) in anhydrous THF (18.5ml) at -78°C under N_2 was added 1.56M *n*-butyl lithium in hexanes (2.47ml, 3.86mmol) dropwise, to produce a yellow colored solution. After stirring at -78°C for 20 min,
- 10 dry $MgBr_2OEt_2$ (1.045g, 4.05mmol) was added as a solid. The resulting heterogeneous mixture was warmed to -45°C and stirred for 15min. The reaction mixture was then recooled to -78°C and a solution of (S)-Alloc-Asp(*t*-Bu)H (946.4mg, 3.68mmol) in THF (18.5ml) was added
- 15 dropwise. The reaction was stirred at -78°C for 30min, warmed to 0°C and stirred for 1h. The resulting homogeneous reaction was warmed to room temperature and stirred for 16h. The reaction was quenched with 5% sodium bicarbonate (3.5ml) then THF was removed *in vacuo*.
- 20 The resulting aqueous residue was extracted with methylene chloride (x6). The combined extracts were washed with brine, dried ($MgSO_4$), filtered and reduced *in vacuo* to give 1.8g of crude product. Flash chromatography (40:60 ethyl acetate/hexane) gave 1.21g
- 25 (81%) of the title compound, an oil, as a mixture of diastereoisomers at C-4: IR (CH_2Cl_2) 3425, 2983, 1725, 1504, 1290, 1157, 1101; 1H NMR ($CDCl_3$) δ 7.35-7.19 (2H, m), 6.89-6.81 (1H, m), 6.00-5.57 (2H, m), 5.32-5.05 (3H, m), 4.68-4.35 (3H, m), 4.01 (3H, s), 2.86-2.59 (2H, m), 1.45 (9H, s), 1.41 (9H, s); ^{13}C NMR ($CDCl_3$) δ
- 30 171.18, 171.09, 165.80, 165.30, 156.71, 156.60, 145.65, 142.76, 142.71, 140.82, 140.72, 133.23, 125.81, 125.72,

- 359 -

118.41, 118.21, 113.07, 112.87, 108.95, 82.16, 70.28, 69.98, 66.52, 66.39, 57.03, 52.57, 52.29, 37.83, 36.86, 28.65. Anal. Calcd. for $C_{20}H_{26}N_2O_7$. $0.6H_2O$: C, 57.57; H, 6.57; N, 6.72. Found: C, 57.49, H, 6.34, N, 6.60.
 5 M.S. (+ FAB); 407 ($M^+ + 1$); 351, 307, 154.

(3*S*, 4*R*, *S*) *t*-Butyl N-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(2-(4-methoxybenzoxazolyl))butanoate (66b), was prepared according to the method described for 66a which afforded 1.29g (26%, 68% based on recovered
 10 starting material) of the title compound as an oil and as a mixture of diastereoisomers at C-4: IR (CH_2Cl_2) 3400, 1725, 1625, 1505, 1369, 1354, 1281, 1263, 1226, 1158, 1092, 1048; 1H NMR ($CDCl_3$) δ 7.34-7.24 (1H, m), 7.16 (1H, d, $J = 8.2$), 6.79 (1H, d, $J = 7.9$), 6.00-5.50
 15 (2H, m), 5.30-5.05 (3H, m), 4.70-4.35 (4H, m), 4.02 (3H, s), 2.90-2.45 (2H, m), 1.45-1.41 (9H, 2 x s). Anal. Calcd. for $C_{20}H_{26}N_2O_7$. $0.4H_2O$: C, 58.07; H, 6.53; N, 6.77. Found: C, 58.09; H, 6.41; N, 6.63. M.S. (+ FAB); 407 ($M^+ + 1$, 88%); 351 (100).

20 (3*S*, 4*R*, *S*) *t*-Butyl N-(N-acetyl-(*S*)-(O-*tert*-butyl-tyrosinyl)-(*S*)-valinyl-(*S*)-alaninyl)-3-amino-4-hydroxy-4-(2-(7-methoxybenzoxazolyl))butanoate (67a). To a stirred solution of the benzoxazole 66a (481.9mg, 1.19mmol) and Ac-Tyr(^tBu)-Val-Ala-OH (586.3mg, 1.30mmol) in methylene chloride (3.5ml) and DMF (3.5ml)
 25 was added bis(triphenylphosphine) palladium (II) chloride (18.0mg), followed by tributyltinhydride (0.80ml, 2.96mmol) dropwise. Hydroxybenzotriazole (320.4mg, 2.37mmol) was added and the mixture cooled to
 30 0°C. 1-Ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (278.2mg, 1.42mmol) was added and the

- 360 -

mixture was allowed to warm to room temperature and stirred for 16.5h. The reaction was diluted with ethyl acetate and washed twice with 1M sodium hydrogensulphate, twice with saturated sodium bicarbonate, water, and brine. The organic layer was dried (MgSO_4), filtered and reduced *in vacuo* to yield 2.0g of crude product. Flash chromatography (95:5 methylene chloride/methanol) gave 844.0mg (94%) of the title compound as a white solid: m.p. 205°C; IR (KBr) 3399, 3304, 2977, 1729, 1643, 1506, 1367, 1290, 1161; ^1H NMR (d_6 -DMSO) δ 8.24-7.78 (4H, m), 7.43-7.32 (2H, m), 7.23 (2H, d, $J = 8.5$), 7.16-7.07 (1H, m), 6.93 (2H, d, $J = 8.5$), 6.52, 6.40 (1H, 2 x d, $J = 5.5$, $J = 5.0$), 5.03, 4.78-4.49, 4.45-4.16 (5H, brt, 2 x m), 4.05, 4.04 (3H, 2 x s), 3.08-2.35 (14H, m), 2.11-1.89 (1H, m), 1.83 (3H, s), 1.49-1.32, 1.15, 1.0-0.81 (27H, s, 2 x m, $J = 7.0$); ^{13}C NMR (d_6 -DMSO) δ 175.55, 175.18, 173.88, 173.75, 173.05, 169.23, 157.28, 148.55, 146.16, 143.21, 136.63, 133.55, 128.87, 127.17, 115.78, 111.92, 84.02, 81.50, 71.40, 61.15, 60.05, 57.79, 53.39, 51.62, 43.76, 40.52, 34.58, 32.52, 31.60, 26.35, 23.11, 22.71, 21.76. Anal. Calcd. for $\text{C}_{39}\text{H}_{55}\text{N}_5\text{O}_{10} \cdot 0.5\text{H}_2\text{O}$: C, 61.40; H, 7.40; N, 9.18. Found: C, 61.43; H, 7.31; N, 9.07. M.S. (+ FAB); 754 ($\text{M}^+ + 1$); 698, 338, 267.

(3*S*, 4*R*,*S*) *t*-Butyl *N*-(*N*-acetyl-(*S*)-(O-*tert*-butyl-tyrosinyl)-(*S*)-valinyl-(*S*)-alaninyl)-3-amino-4-hydroxy-4-(2-(4-methoxybenzoxazolyl))butanoate (67b), was prepared according to the method described for 67a which afforded 1.05g (94%) of the title compound as a fine white powder: m.p. 210-213°C (dec); IR (KBr) 3284, 2977, 1736, 1691, 1632, 1536, 1505, 1452, 1392, 1367, 1258, 1236, 1161, 1091; ^1H NMR (d_6 -DMSO) δ 8.20-

- 361 -

7.75 (4H, m), 7.40-7.10 (4H, m), 7.00-6.80 (3H, m),
 6.45, 6.34 (1H, 2 x d, $J = 5.3$, $J = 5.0$), 5.00-4.10
 (5H, m), 4.00, 3.99 (3H, 2 x s), 3.00-2.25 (4H, m),
 1.95 (1H, m), 1.78 (3H, s), 1.39-0.80 (27H, m). Anal.
 5 Calcd. for $C_{39}H_{55}N_5O_{10}$. $0.5H_2O$: C, 61.40; H, 7.40; N,
 9.18. Found: C, 61.58; H, 7.38; N, 8.91. M.S.
 (+ FAB); 754 ($M^+ + 1$, 30%); 72 (100).

(3S) t-Butyl N-(N-acetyl-(S)-(O-tert-butyl-tyrosinyl)-
 (S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(7-
 10 methoxybenzoxazolyl))-4-oxobutanoate (68a). The Dess-
 Martin reagent (1.082g, 2.55mmol) (Ireland et al., J. Org. Chem., 58, p. 2899 (1993); Dess et al., J. Org. Chem., 48, pp. 4155-4156 (1983)) was added to a stirred
 suspension of the alcohol 67a (641.0mg, 0.85mmol) in
 15 methylene chloride (46.0ml). The resulting mixture was
 stirred for 1h before being partitioned between
 saturated sodium thiosulphate: saturated sodium
 bicarbonate (1:1, 86.0ml) and ethyl acetate (86.0ml).
 The resultant organic phase was washed in turn with
 20 saturated sodium thiosulphate: saturated sodium
 bicarbonate (1:1), saturated sodium bicarbonate, and
 brine. The organic phase was dried ($MgSO_4$), filtered
 and reduced *in vacuo* to give 660.0mg of crude product.
 Flash chromatography (94:6 methylene chloride/methanol)
 25 gave 636.0mg (100%) of the title compound as a white
 solid: m.p. 209°C; $[\alpha]_D^{24} -21.8^\circ$ (c 0.16, methanol); IR
 (KBr) 3395, 3294, 2977, 1722, 1641, 1535, 1505, 1161;
 1H NMR ($CDCl_3$) δ 8.43-8.16 (1H, m), 7.97-7.62 (2H, m),
 7.49-7.14 (3H, m), 7.08-6.95 (3H, m), 6.89-6.73 (2H,
 30 m), 5.81-5.68 (1H, m), 5.16-4.86 (2H, m), 4.53 (1H,
 brt), 4.03 (3H, s), 3.16-2.84 (4H, m), 2.11-1.84 (4H,
 m), 1.46-1.14 (21H, m), 0.92-0.78 (6H, m); ^{13}C NMR

- 362 -

(CDCl₃) δ 186.28, 173.39, 171.90, 171.19, 171.03, 169.89, 156.43, 154.75, 146.32, 142.88, 140.98, 132.31, 130.54, 126.98, 124.73, 114.95, 111.42, 82.44, 78.71, 58.92, 57.20, 54.91, 53.47, 48.77, 39.43, 38.15, 32.79, 29.44, 28.60, 23.55, 20.27, 19.70, 19.34. M.S. (+ FAB); 752 ($M^+ + 1$); 696, 336, 265.

(3S) t-Butyl N-(N-acetyl-(S)-(O)-tert-butyl-tyrosinyl)-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(4-methoxybenzoxazolyl))-4-oxobutanoate (68b), was prepared according to the method described for the ketone 68a which afforded 420mg (55%) of the title compound as a white solid: m.p. 211-213°C (dec); $[\alpha]_D^{24}$ -23.9° (c 0.82, methanol); IR (KBr) 3277, 3075, 1723, 1690, 1632, 1530, 1506, 1392, 1366, 1269, 1234, 1160, 1094; ¹H NMR (CDCl₃) δ 8.15 (1H, brs), 7.7 (2H, brs), 7.46 (1H, t, $J = 8.3$), 7.24 (2H, d, $J = 8.3$), 7.10 (1H, brs), 7.03 (2H, d, $J = 8.3$), 6.83 (3H, m), 5.74 (1H, q, $J = 6.9$), 5.00 (2H, m), 4.51 (1H, t, $J = 7.0$), 4.07 (3H, s), 3.20-2.95 (4H, m), 2.00 (4H, m), 1.42 (3H, d, $J = 6.8$), 1.35 (9H, s), 1.23 (9H, s), 0.86 (6H, d, $J = 6.7$). M.S. (+ FAB); 752 ($M^+ + 1$, 7%); 72 (100).

Sub
A10

(3S) N-(N-Acetyl-(S)-tyrosinyl-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(7-methoxybenzoxazolyl))-4-oxobutanoate (69a; R). A solution of the ester 68a (600.0mg, 0.80mmol) in a 1:1 mixture of methylene chloride and trifluoroacetic acid (65.0ml) was stirred for 1h under a dry atmosphere of N₂. The solution was then reduced *in vacuo*, taken up in ether and reduced again. This process was repeated six times to afford the crude product as an off white solid. Flash chromatography (gradient 95:5 to 80:20 methylene

- 363 -

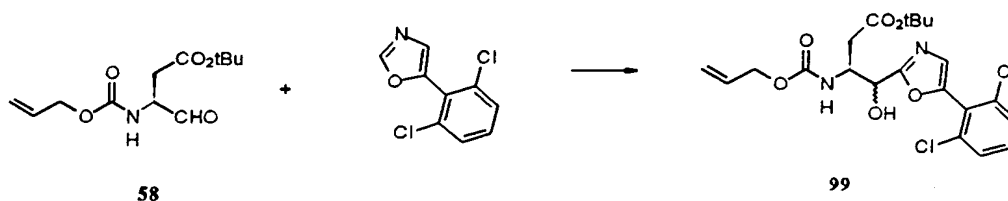
chloride/methanol) gave 420.8mg (83%) of the title compound as a hygroscopic white solid. The product existed as a mixture of three isomers in CD₃OD, consisting of the keto form (c 50%), and its acycloxy keto form (two isomers at C-4, c 50%): m.p. decomposes above 150°C; $[\alpha]_D^{24} -33.2^\circ$ (c 0.17, methanol); IR (KBr) 3300, 1715, 1658, 1650, 1531, 1517, 1204; ¹H NMR (CD₃OD) δ 7.46-7.19 (2H, m), 7.16-6.91 (3H, m), 6.70-6.59 (2H, m), 5.62-5.49 (1H, m), 5.00-4.72 (1H, obscured m), 4.69-4.51 (1H, m), 4.49-4.08 (2H, m), 4.05-3.89 (3H, m), 3.16-2.47 (4H, m), 2.05-1.78 (4H, m), 1.41-1.11, 1.05-0.70 (9H, 2 x m). Anal. Calcd. for C₃₁H₃₇N₅O₁₀ · 3H₂O: C, 53.67; H, 6.25; N, 10.10. Found: C, 53.76; H, 5.56; N, 10.28. M.S. (+ FAB); 640 (M⁺ + 1); 435, 147.

(3S) t-Butyl N-(N-acetyl-(S)-tyrosinyl-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(4-methoxybenzoxazolyl))-4-oxobutanoate (69b; S), was prepared according to the method described for the acid 69a which afforded the hygroscopic title compound 252mg (96%). The product existed as a mixture of three isomers in CD₃OD, consisting of the keto form, and its acycloxy ketal form (two isomers at C-4). The product existed as a single isomer in d-6 DMSO: m.p. 200-203°C (dec.); $[\alpha]_D^{24} -38.0^\circ$ (c 0.23, methanol); IR (KBr) 3289, 2968, 1718, 1713, 1658, 1634, 1548, 1517, 1506, 1461, 1453, 1393, 1369, 1268, 1228, 1174, 1092; ¹H NMR (d₆-DMSO) δ 9.20 (1H, brs), 8.71 (1H, d, J = 6.2), 8.10 (2H, m), 7.83 (1H, d, J = 8.7), 7.61 (1H, t, J = 8.2), 7.46 (1H, d, J = 8.2), 7.08 (3H, m), 6.65 (2H, d, J = 8.3), 5.50 (1H, q, J = 6.5), 4.50 (1H, m), 4.37 (1H, m), 4.20 (1H, m), 4.05 (3H, s), 3.09-2.77 (4H, m), 1.94 (1H, m), 1.79

- 364 -

Sub
A''

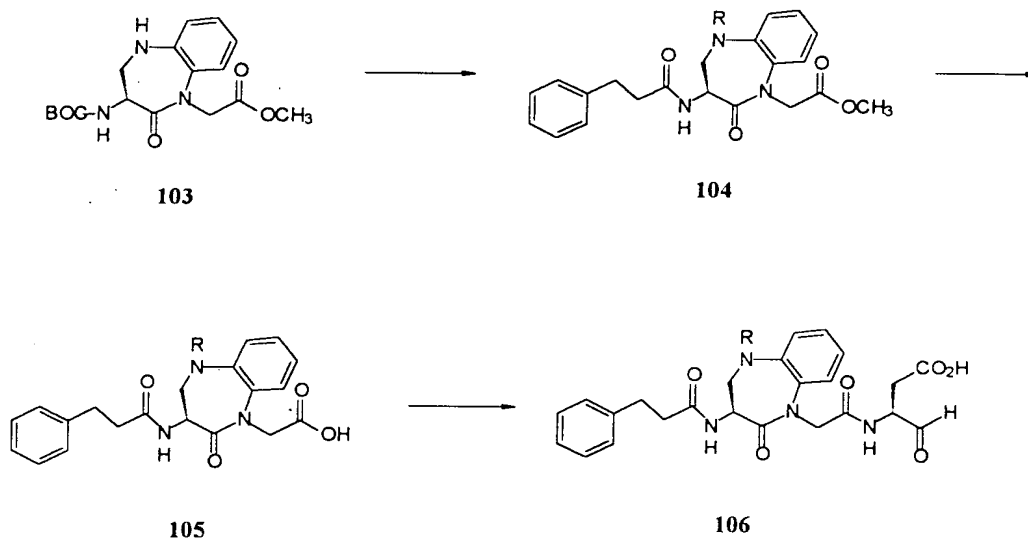
(3H, s), 1.23 (3H, d, $J = 7.0$), 0.82 (6H, m). Anal. Calcd. for $C_{31}H_{37}N_5O_{10} \cdot 1.5H_2O$: C, 55.85; H, 6.05; N, 10.51. Found: C, 55.21; H, 5.69; N, 10.13. M.S. (+ FAB); 640 ($M^+ + 1$, 22%); 107 (100).



- 5 **3(S)-(Allyloxycarbonyl)-amino-4-[(2,6-dichloro-phenyl)-oxazol-2-yl]-4(R,S)-hydroxy-butyric acid tert-butyl ester (99).** A solution of 5-(2,6-Dichlorophenyl)oxazole (2.71g, 12.7mmol; prepared by a similar method described in Tet. Lett. 23, p. 2369
- 10 (1972)) in tetrahydrofuran (65mL) was cooled to -78°C under a nitrogen atmosphere. To this solution was added n-butyl lithium (1.5M solution in hexanes, 8.5mL, 13.3mmol) and stirred at -78°C for 30min. Magnesium bromide etherate (3.6g, 13.9mmol) was added and the
- 15 solution was allowed to warm to -45°C for 15min. The reaction was cooled to -78°C and aldehyde **58** (3.26g, 12.7mmol; Graybill et al., Int. J. Protein Res., 44, pp. 173-182 (1993)) in tetrahydrofuran (65mL) was added dropwise. The reaction was stirred for 25min., then
- 20 allowed to warm to -40°C and stirred for 3h, and then at room temperature for 1h. The reaction was quenched with 5% NaHCO_3 (12mL) and stirred for 3h. The tetrahydrofuran was removed in vacuo and the resulting residue was extracted with dichloromethane. The
- 25 organic layer was washed with saturated sodium chloride solution and dried over magnesium sulfate, filtered, and concentrated to yield 6.14g of the title compound.

- 365 -

Purification gave 4.79g (80%) of **99**: ^1H NMR (CDCl_3) δ 1.45(s, 9H), 2.7-2.5(m, 2H), 2.8(dd, 1H), 4.2, 4.4(2 x d, 1H), 4.7-4.5(m, 3H), 5.35-5.1(m, 2H), 5.6, 5.7(2 x d, 1H), 6.0-5.8(m, 1H), 7.2(d, 1H), 7.3(m, 1H), 7.4(m, 2H).



a R = H

b R = $\text{COCH}_2\text{CH}_2\text{Ph}$ c R = CH_2Ph

[2-Oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-yl]acetic acid methyl ester (**104a**). Anhydrous hydrogen chloride was bubbled into a solution of (3(S)-tert-butoxycarbonylamino-2-oxo-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-yl)acetic acid methyl ester (**103**, 1g, 2.86 mmol) in 25 ml of ethyl acetate for 2 minutes then stirred for 1 hour at room temperature. The reaction was evaporated to give 2-oxo-3(S)-amino-2,3,4,5-

- 366 -

tetrahydrobenzo[b][1,4]diazepin-1-yl acetic acid methyl ester hydrochloride as a white solid.

The hydrochloride salt and hydrocinnamic acid (0.47 g, 3.15 mmol) were dissolved into 20 ml of

5 dimethylformamide and cooled to 0 °C.

Diisopropylethylamine (1 ml, 5.72 mmol) was added to the solution followed by the addition of N-

hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. After stirring for 18

10 hours at room temperature, the mixture was diluted with 150 ml of ethyl acetate and washed with 10% sodium hydrogen sulfate, 10% sodium bicarbonate, and brine.

The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to a crude solid that

15 was purified by flash chromatography eluting with 7:3 ethyl acetate/dichloromethane to afford 600 mg (55%) of the title compound as a white solid. ¹H NMR (CDCl₃) δ 7.3-6.85 (9H, m), 6.55-6.0 (1H, d), 4.88-4.82 (1H, m), 4.72-4.65 (1H, d), 4.28-4.22 (1H, m), 3.95-3.9 (1H, m), 3.78 (3H, s), 3.65 (1H, br. s), 3.28-3.2 (1H, m), 2.95-2.84 (2H, m), 2.55-2.4 (2H, m).

(3(S)-(3-Phenylpropionylamino)-2-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl)acetic acid (105a).

(3(S)-(3-Phenylpropionylamino)-2-oxo-2,3,4,5-

25 tetrahydro-benzo[b][1,4]diazepin-1-yl)acetic acid methyl ester (**104a**) was dissolved in 90% methanol.

Lithium hydroxide hydrate was added to the reaction and the reaction was stirred at room temperature for 4 h.

The reaction was evaporated in vacuo to give a white

30 solid. This was dissolved in 20 ml of water and acidified to pH 5 and extracted with ethyl acetate to afford 304 mg (88%) of the title compound as a white

- 367 -

solid. ^1H NMR (CDCl_3) δ 7.5-6.9 (11H, m), 4.92-4.8 (1H, m), 4.7-4.58 (1H, d), 4.38-4.25 (1H, d), 3.88-3.78 (1H, m), 3.45-3.25 (1H, m), 3.05-2.85 (2H, m), 2.55-2.45 (2H, m).

5 4-Oxo-3(S)-{2-[2-oxo-3(S)-(3-phenylpropionylamino)-
2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-
ylacetyl amino}butyric acid (106a). N-[1-(2-Benzyloxy-
5-oxotetrahydrofuran-3-ylcarbamoyl-methyl)-2-oxo-
2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-3-
10 phenylpropionamide was prepared from 105a by the
procedure used to prepare compound H (stepA) to afford
390 mg (93%) of the product as diastereomers. ^1H NMR
(CD_3OD) δ 7.58-7.22 (14H, m), 5.78-5.73 (0.5 H, d), 5.64
(0.5 H, s), 5.0-4.72 (4H, m), 4.54-4.42 (2H, m), 3.82-
15 3.76 (0.5 H, m), 3.68-3.62 (0.5 H, m), 3.28-3.21 (0.5H,
m), 3.19-3.12 (0.5H, m), 3.07-2.98 (2H, m), 2.78-2.48
(4H, m).

The resulting product was converted to 106a by the
method described to prepare compound H (StepD) to
20 afford the title compound as a white solid (17%): ^1H
NMR (CD_3OD) δ 7.54-6.98 (9H, m), 5.58-5.44 (1H, m), 4.8-
4.2 (4H, m), 3.96-3.3 (2H, m), 3.30-3.05 (1H, m), 2.98-
2.25 (5H, m).

[2-Oxo-5-(3-phenylpropionyl)-3(S)-(3-
25 phenylpropionylamino)-2,3,4,5-
tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid methyl
ester (104b). Anhydrous hydrogen chloride was bubbled
into a solution of (3(S)-tert-butoxycarbonylamino-2-
oxo-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-
30 yl)acetic acid methyl ester (103, 1g, 2.86mmol) in 25

- 368 -

ml of ethyl acetate for 2 minutes then stirred for 1 hour at room temperature. The reaction was evaporated to give 2-oxo-3(S)-amino-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl acetic acid methyl ester hydrochloride as a white solid.

The hydrochloride salt was suspended into 20 ml of dichloromethane and cooled to 0 °C. Triethylamine (1.6 ml, 11.5 mmol) was added to the suspension followed by the dropwise addition of dihydrocinnamoyl chloride (0.9 ml, 6 mmol). The mixture was warmed to room temperature and stirred for 18 hours. The mixture was diluted with 25 ml of dichloromethane and washed twice with 50 ml of water and once with 50 ml of brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to give a viscous, yellow oil that was purified by flash chromatography eluting with 1:1 ethyl acetate/dichloromethane to afford 1.35 g (92%) of the title product as a white solid. ¹H NMR (CDCl₃) δ 7.45-7.02 (14 H, m), 6.37-6.32 (1H, d), 4.78-4.72 (1H, m), 4.52-4.3 (3H, m), 3.82-3.77 (1H, m), 3.74 (3H, s), 3.03-2.87 (4H, m), 2.58-2.45 (2H, m), 2.45-2.35 (1H, m), 2.25-2.16 (1H, m).

[2-Oxo-5-(3-phenylpropionyl)-3-(3(S)-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid (105b). [2-Oxo-5-(3-phenylpropionyl)-3-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid methyl ester (104b; 680 mg, 1.32 mmol) was hydrolyzed by the procedure used to hydrolyze 105a to afford 645 mg (98%) of the title compound as a white solid. ¹H NMR (CDCl₃) δ 7.58 (1H, br. s), 7.5-7.42 (1H, m), 7.35-6.95 (14H,

- 369 -

m), 4.95-4.88 (1H, m), 4.64-4.55 (1H, d), 4.54-4.45 (1H, t), 4.15-4.05 (1H, d), 3.75 (1H, m), 3.05-2.75 (4H, m), 2.58-2.45 (2H, m), 2.45-2.28 (1H, m), 2.25-2.14 (1H, m).

- 5 2-Oxo-3(S)-{2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenyl-propionyl-amino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetyl-amino}butyric acid (106b). [2-Oxo-5-(3-phenylpropionyl)-3-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid and 3-amino-4-oxobutyric acid tert-butylester semicarbazone were coupled by the procedure used in the preparation of compound K (step A) to give 350 mg (85%) of a white solid. ¹H NMR (CDCl₃) δ 9.05 (1H, br. s), 7.58-7.55 (1H,d), 7.5-7.35 (1H, m), 7.35-6.95 (14 H, m), 6.75-6.72 (1H, d), 6.25 (1H, br. s), 5.25 (1H, br. s), 4.95-4.88 (1H, m), 4.8-4.72 (1H, m), 4.55-4.4 (2H, m), 3.92-3.88 (1H, d), 3.73-3.68 (1H, m), 2.95-2.8 (4H, m), 2.8-2.72 (1H, m), 2.62-2.55 (1H, m), 2.55-2.45 (2H, m), 2.4-2.32 (1H, m), 2.2-2.12 (1H, m), 1.45 (9H, s).
- 10 4-Oxo-3-{2-[2-oxo-5-(3-phenylpropionyl)-3-(3-phenyl-propionyl -amino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetyl-amino}butyric acid tert-butyl ester semicarbazone was deprotected as described in the preparation of compound K (step C) to give 118 mg (47%) of the title compound as a white solid. ¹H NMR (CD₃OD) δ 7.48-6.95 (14 H, m), 4.65-4.15 (6H, m), 3.5-3.4 (1H, m), 2.85-2.72 (4H, m), 2.65-2.5 (1H, m), 2.5-2.34 (3H, m), 2.34-2.15 (2H, m).
- 15 [5-Benzyl-2-oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-yl]acetic acid
- 20
- 25
- 30

- 370 -

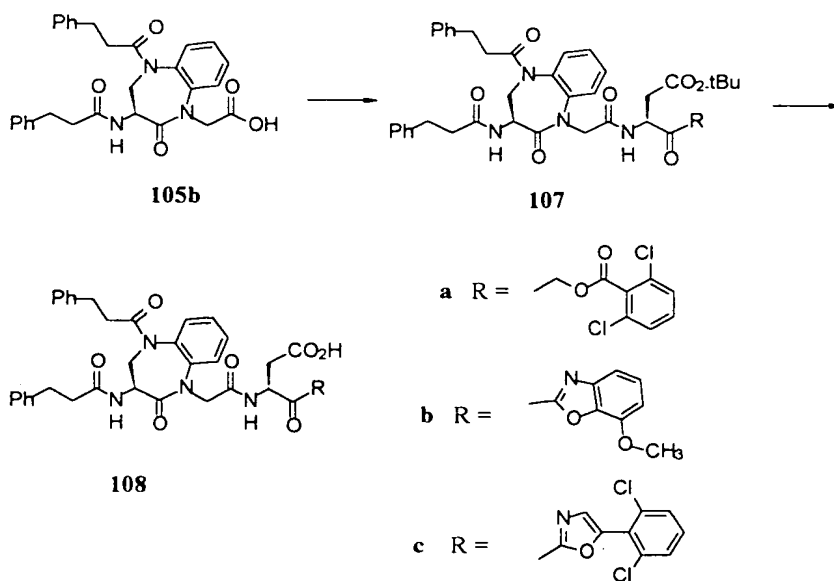
methyl ester (104c). [2-Oxo-3-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo-
[b][1,4]diazepin-1-yl]acetic acid methyl ester (104a;
500 mg, 1.31 mmol), calcium carbonate (155 mg, 1.58
5 mmol), and benzyl bromide (170 μ l, 1.44 mmol) were
taken into 10 ml of dimethylformamide and heated to 80
°C for 8 hours. The mixture was diluted with 150 ml of
ethyl acetate and washed 4 times with 50 ml of water.
The organic layer was dried over anhydrous sodium
10 sulfate, filtered, and evaporated to give a viscous,
yellow oil that was purified by flash chromatography
eluting with dichloromethane/ethyl acetate (8:2) to
give 460 mg (75%) of the title compound as a white
solid. ^1H NMR (CDCl_3) δ 7.34-7.05 (14 H, m), 6.32-6.28
15 (1H, d), 4.84-4.76 (1H, d), 4.76-4.70 (1H, m), 4.43-
4.37 (1H, d), 4.26-4.18 (1H, d), 4.06-4.00 (1H, d),
3.79 (3H, s), 3.45-3.37 (1H, m), 3.02-2.95 (1H, m),
2.90-2.82 (2H, m), 2.5-2.34 (2H, m).

[5-Benzyl-2-oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-
20 tetrahydro-benzo[b][1,4]diazepin-1-yl]acetic acid
(105c) was prepared by the hydrolysis of the ester
(102c) by the procedure reported in Example 105a to
give 450 mg (98%) of the title compound as a white
solid: ^1H NMR (CD_3OD) δ 7.5-7.05 (14 H, m), 6.4 (1H,
25 br. s), 4.85-4.55 (2H, m), 4.5-4.21 (2H, m), 4.12-3.92
(1H, d), 3.45-3.3 (1H, m), 3.1-2.8 (3H, m), 2.55-2.28
(3H, m).

3(S)-{2-[5-Benzyl-2-oxo-3-(3(S)-phenylpropionylamino)-
2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-
30 acetylamino}-4-oxobutyric acid (106c). [5-Benzyl-2-

- 371 -

oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydro-
 benzo[b[1,4]diazepin-1-yl]acetic acid and 3(S)-amino-4-
 oxobutyric acid tert-butylester semicarbazone were
 coupled by the procedure used in the preparation of
 5 compound **K** (step A) and to afford 260 mg (85%) of a
 white solid: ^1H NMR (CD_3OD) δ 7.35-7.0 (15 H, m), 4.94-
 4.88 (1H, m), 4.68-4.58 (1H, d), 4.57-4.52 (1H, m),
 4.41-4.34 (1H, d), 4.3-4.23 (1H, d), 4.1-4.04 (1H, d),
 3.18-3.11 (1H, m), 3.09-2.98 (1H, m), 2.78-2.72 (2H,
 10 t), 2.65-2.57 (1H, m), 2.42-2.33 (3H, m).
 3(S)-{2-[5-Benzyl-2-oxo-3(S)-(3-phenylpropionylamino)-
 2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-
 acetyl-amino}-4-oxobutyric acid tert-butyl ester
 semicarbazone was deprotected as described in the
 15 preparation of compound **K** (step C) to give 168 mg (81%)
 of the title compound as a white solid. ^1H NMR (CD_3OD)
 δ 7.37-7.0 (14H, m), 4.75-4.62 (1H, m), 4.6-4.45 (2H,
 m), 4.4-4.21 (2H, m), 4.15-3.95 (2H, m), 3.15-3.0 (2H,
 m), 2.82-2.67 (2H, m), 2.65-2.52 (1H, m), 2.5-2.32 (3H,
 20 m).



- 372 -

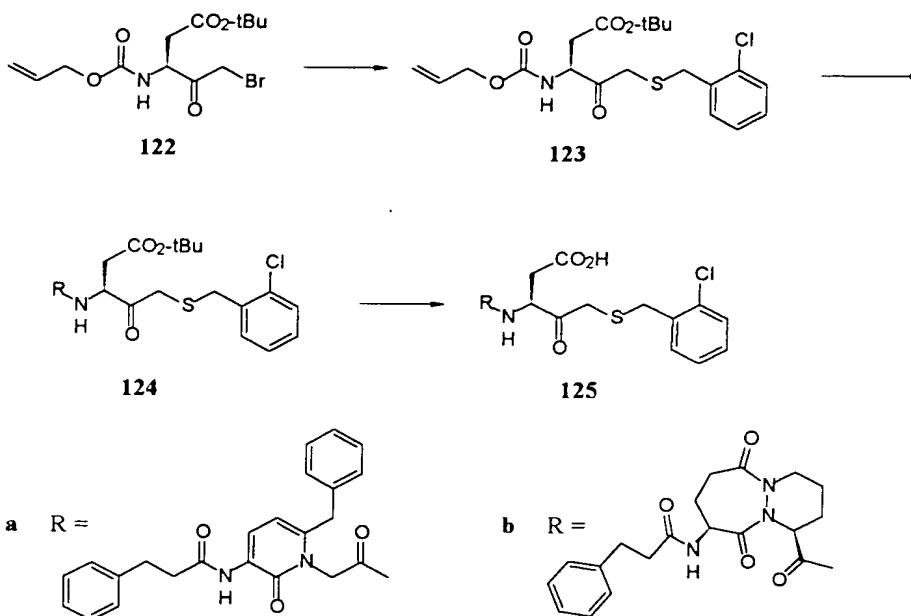
2,6-Dichlorobenzoic acid 4-tert-butoxycarbonyl-2-oxo-3(S)-{2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetyl-amino}butyl ester (107a). The resulting semicarbazone was prepared by the coupling of compound 105b and t-butyl 3-(allyloxycarbonylamino)-4-oxo-5-(2,6-dichlorobenzoyloxy)pentanoate (WO 93 16710) as described in compound 56a to give 256 mg (58%) of the title compound as a white solid. ¹H NMR (CDCl₃) δ 7.45-7.04 (17H, m), 6.45-6.34 (2H, m), 5.28-5.21 (1H, m), 5.1-5.0 (1H, m), 4.95-4.90 (1H, m), 4.75-4.70 (1H, m), 4.55-4.44 (1H, m), 4.32-4.22 (1H, dd), 3.99-3.85 (1H, dd), 3.85-3.76 (1H, m), 3.06-2.83 (5H, m), 2.83-2.74 (1H, m), 2.6-2.44 (2H, m), 2.43-2.33 (1H, m), 2.24-2.15 (1H, m), 1.45 (9H, s).

2,6-Dichlorobenzoic acid 4-carboxy-2-oxo-3(S)-{2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetyl-amino}butyl ester (108a) was prepared from 107a by the method described for compound 57a which afforded 156 mg (68%) of the title compound as a white solid. ¹H NMR (CD₃OD) δ 7.5-6.9 (17H, m), 5.16-5.02 (1H, dd), 4.88-4.71 (2H, m), 4.62-4.44 (2H, m), 4.42-4.28 (2H, m), 4.27-4.18 (1H, m), 3.47-3.41 (1H, m), 2.90-2.60 (5H, m), 2.46-2.4 (2H, m), 2.39-2.18 (2H, m).

4-(7-Methoxybenzoxazol-2-yl)-4-oxo-3(S)-{2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetyl-amino}butyric acid (108b) was prepared by the method

- 373 -

described for compound **69a** to give the title compound (50%) as a white solid. ^1H NMR (CD_3OD) δ 7.41-6.88 (17H, m), 5.6-5.55 (0.5H, t), 5.48-5.43 (0.5H, t), 4.64-4.45 (2H, m), 4.45-4.30 (1H, m), 3.93 (1.5H, s), 3.90 (1.5H, s), 3.47-3.34 (1H, m), 3.10-2.85 (2H, m), 2.84-2.63 (5H, m), 2.6-2.4 (2H, m), 2.3-2.1 (2H, m).



t-Butyl (3S) N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenylmethylthio)-4-oxo-pentanoate (123).

Potassium fluoride (273mg, 4.70mmol) and then 2-chlorophenylmethyl thiol (373mg, 2.35mmol) were added to a stirred solution of (3S) t-butyl N-(allyloxycarbonyl)-3-amino-5-bromo-4-oxo-pentanoate (**122**; 749mg, 2.14mmol; WO 93 16710) in dimethylformamide (20ml). The mixture was stirred for 3.5h, quenched with water (50ml) and extracted with ethyl acetate (2 x 50ml). The combined organic extracts were washed with water (4 x 50ml) then brine

- 374 -

(50ml). They were dried (MgSO₄) and concentrated to afford an oil which was purified by flash chromatography (10-35% ethyl acetate/hexane) to afford 832 mg (91%) of a colourless solid: mp. 45-6 °C; $[\alpha]_D^{20}$ -19.0° (c 1.0, CH₂Cl₂); IR (film) 3340, 2980, 2935, 1725, 1712, 1511, 1503, 1474, 1446, 1421, 1393, 1368, 1281, 1244, 1157, 1052, 1040, 995, 764, 739; ¹H NMR (CDCl₃) δ 7.36 (2H, m), 7.21 (2H, m), 5.91 (2H, m), 5.27 (2H, m), 4.76 (1H, m), 4.59 (2H, d), 3.78 (2H, s), 3.36 (2H, m), 2.91 (1H, dd), 2.74 (1H, dd), 1.43 (9H, s). Anal. Calcd for C₂₀H₂₆ClNO₅S: C, 56.13; H, 6.12; N, 3.27; S, 7.49. Found: C, 56.08; H, 6.11; N, 3.26; S, 7.54. MS (C.I.) 430/28 (M⁺ + 1, 3%), 374/2 (100).

t-Butyl (3S) 3(2(6-benzyl-1,2-dihydro-2-oxo-3(3-phenylpropionylamino)-1-pyridyl)acetylamino-5-(2-chlorophenylmethylthio)-4-oxopentanoate (124a). 6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionylamino)-pyridyl acetic acid (**52b**; 300mg, 0.76mmol) in THF (7ml) was stirred with 1-hydroxybenzotriazole (205mg, 1.52mmol) and 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride). After 3 min, water (12 drops) was added and the mixture stirred 10min then treated with t-butyl (3S) N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenylmethylthio)-4-oxopentanoate (**123**) (325mg, 0.76mmol), bis (triphenylphosphine) palladium II chloride (20mg) and tributyltin hydride (0.6ml, 2.28mmol). The mixture was stirred for 5h at room temperature, poured into ethyl acetate and washed with aqueous 1M HCl (x2), aqueous sodium bicarbonate, brine, dried (MgSO₄) and concentrated. The residue was triturated with pentane and the supernatant discarded. Chromatography (silica gel, 50% ethyl acetate/hexane)

- 375 -

afforded a colourless foam (439mg, 81%): $[\alpha]_D^{21} -18.3^\circ$ (c 0.5, CH_2Cl_2); IR (KBr) 3356, 3311, 1722, 1689, 1646, 1599, 1567, 1513, 1367, 1154; ^1H NMR (CDCl_3) δ 8.39 (1H, d), 8.23 (1H, s), 7.24 (14H, m), 6.16 (1H, d), 4.95 (1H, m), 4.63 (2H, m), 4.02 (2H, s), 3.74 (2H, s), 3.27 (2H, s), 2.85 (6H, m), 1.40 (9H, s). Anal. Calcd for $\text{C}_{39}\text{H}_{42}\text{ClN}_3\text{O}_6\text{S}$: C, 65.39; H, 5.91; N, 5.87. Found: C, 65.51; H, 5.99; N, 5.77.

t-Butyl[3S(1S,9S)]-3-(6,10-dioxo-1,2,3,4,7,8,9,10-octahydro)-9-(3-phenylpropionylamino)-6H-pyridazine[1,2-a][1,2]diazepine-1-carboxamido-5-(2-chlorophenylmethylthio)-4-oxopentanoate (124b) was prepared by a similar method as 124a from the thioether 123 and 3S(1S,9S)-3-(6,10-dioxo-1,2,3,4,7,8,9,10-octahydro)-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid (45a) to afford 452mg (50%) of colourless foam: mp 55-7 °C; $[\alpha]_D^{22} -94.0^\circ$ (c 0.12, CH_2Cl_2); IR (KBr) 3288, 2934, 1741, 1722, 1686, 1666, 1644, 1523, 1433, 1260, 1225, 1146, 757; ^1H NMR (CDCl_3) δ 7.35 (3H, m), 7.20 (7H, m), 6.46 (1H, d), 5.21 (1H, m), 4.97 (2H, m), 4.56 (1H, m), 3.75 (2H, s), 3.25 (3H, m), 2.93 (5H, m), 2.71 (1H, dd), 2.55 (2H, m), 2.30 (1H, m), 1.92 (3H, m), 1.66 (2H, m), 1.42 (9H, s). Anal. Calcd for $\text{C}_{35}\text{H}_{43}\text{ClN}_4\text{O}_7\text{S} \cdot 0.25\text{H}_2\text{O}$: C, 59.73; H, 6.23; Cl, 5.04; N, 7.96; S, 4.56. Found: C, 59.73; H, 6.19; Cl, 5.10; N, 7.79; S, 4.58. MS (-FAB) 697 (M-1, 100).

Sub

A¹²

(3S) 3(2(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionylamino)-1-pyridyl)acetyl-amino-5-(2-chlorophenylmethylthio)-4-oxopentanoic acid (125a).

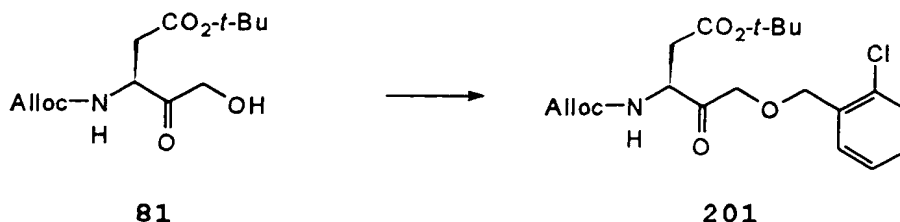
- 376 -

Sub
A12

t-Butyl-3(2(6-benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionylamino)-1-pyridyl)acetyl-amino-5-(2-chlorophenylmethylthio)-4-oxopentanoate (**124a**) (400mg, 0.56mmol) in dichloromethane (3ml) at 0 °C was treated with trifluoroacetic acid (3ml) and stirred at 0 °C for 1h and room temperature for 0.5h. The solution was concentrated then redissolved in dichloromethane and reconcentrated. This procedure was repeated three times. The residue was stirred in ether for 1hr and filtered to yield a colourless solid (364mg, 99%): mp. 165-7 °C; $[\alpha]_D^{22}$ -27.7 ° (c 0.2, CH₂Cl₂); IR (KBr) 3289, 1712, 1682, 1657, 1645, 1593, 1562, 1527, 1497, 1416, 1203, 1182; ¹H NMR (CDCl₃) δ 8.47 (1H, d), 8.21 (1H, s), 7.70 (1H, d), 7.22 (14H, m), 6.24 (1H, d), 5.03 (1H, m), 4.65 (2H, m), 4.06 (2H, s), 3.69 (2H, m), 3.23 (2H, m), 2.88 (6H, m).

[3S(1S,9S)]-3-(6,10-dioxo-1,2,3,4,7,8,9,10-octahydro)-9-(3-phenylpropionyl-amino)-6H-pyridazine[1,2-a][1,2]diazepine-1-carboxamido-5-(2-chlorophenyl-methylthio)-4-oxopentanoic acid (**125b**), was prepared by a similar method as **125a** from the t-butyl ester **124b** to afford 362mg (93%) of colourless powder: mp 76-80 °C; $[\alpha]_D^{21}$ -134 ° (c 0.10, MeOH); IR (KBr) 3309, 2935, 1725, 1658, 1528, 1445, 1417, 1277, 1219, 1175; ¹H NMR (D₆-DMSO) δ 8.80 (1H, d), 8.19 (1H, d), 7.31 (9H, m), 5.09 (1H, m), 4.74 (1H, m), 4.63 (1H, m), 4.35 (1H, m), 3.76 (2H, m), 3.28 (3H, m), 2.80 (5H, m), 2.52 (4H, m), 2.16 (2H, m), 1.90 (3H, m). Anal. Calcd for C₃₁H₃₅Cl₂N₄O₇S. 0.25H₂O: C, 57.49; H, 5.53; N, 8.65; S, 4.95. Found: C, 57.35; H, 5.43; N, 8.45; S, 4.88. MS (-FAB) 641 (M-1, 100).

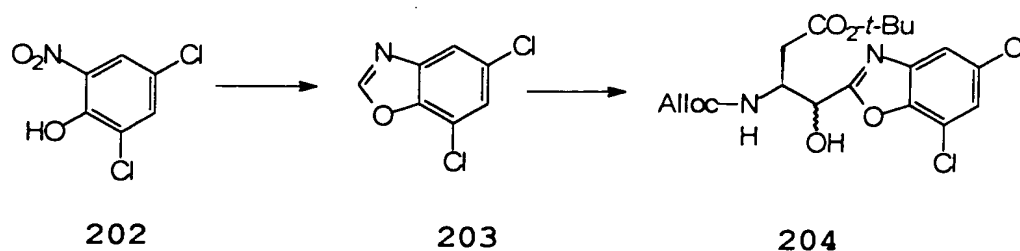
- 377 -



2-Chlorophenylmethyliodide. A mixture of 2-chlorophenylmethylobromide (4g, 19.47mmol) and NaI (14g, 97.33mmol) in acetone (40ml) was stirred under reflux for 1 hour. The reaction mixture was cooled, filtered and concentrated *in vacuo*. The residue was triturated with hexane and filtered. The solution was concentrated *in vacuo*, and the resulting oil purified by flash chromatography (silica, hexane) to afford the title compound (4.67g, 63%) as an oil: ^1H NMR (CDCl_3) δ 7.34 (4H, m), 4.54 (2H, s).

(3S) t-Butyl N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenylmethoxy)-4-oxopentanoate (201). (3S) t-Butyl N-(allyloxycarbonyl)-3-amino-5-hydroxy-4-oxopentanoate (**81**, Chapman, et al., Bioorg. & Med. Chem. Lett., 2, pp. 613-618 (1992) 0.144g, 0.5mmol) and 2-chlorophenylmethyliodide (0.569g, 1.5mmol) in CH_2Cl_2 (4ml) were stirred vigorously with silver oxide (0.231g, 1mmol) and heated at 38 °C for 40 hours. The reaction mixture was cooled, filtered and the filtrate evaporated. The residue was purified by flash chromatography (silica, 0-20% ethylacetate in hexane) to afford the product as a colourless oil (0.138g, 67%): $[\alpha]_{\text{D}}^{24} +3.9^\circ$ (c 1.3, CH_2Cl_2); ^1H NMR (CDCl_3) δ 7.37 (4H, m), 5.88 (2H, m), 5.26 (2H, m), 4.69 (2H, s), 4.57 (3H, m), 4.50 (1H, d), 4.35 (1H, d), 3.03 (1H, dd), 2.76 (1H, dd), 1.42 (9H, s).

- 378 -



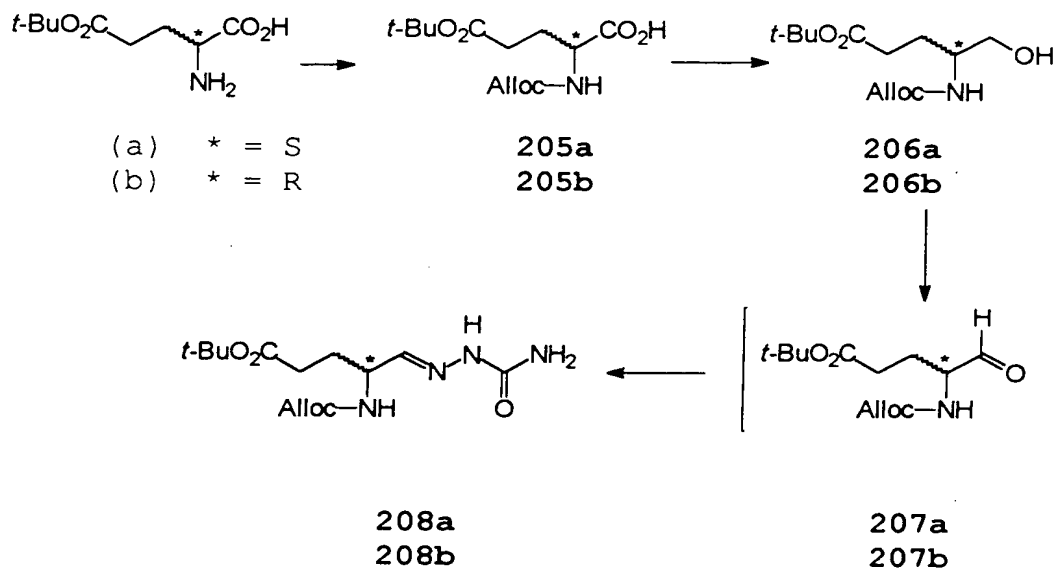
5,7-Dichlorobenzoxazole (203). A solution of 2,4-dichloro-6-nitrophenol (202, 40g containing 20% moisture) in EtOAc (500ml) was dried using MgSO_4 , filtered and the filter cake washed with a little EtOAc. Platinum on carbon (5% sulphided - 2g) was added and the mixture hydrogenated until uptake of H_2 ceased. Triethyl orthoformate (160ml) and p-toluene sulphonic acid (160mg) were added and the mixture refluxed for 4h. After cooling and removal of spent catalyst by filtration the solution was washed with sat. NaHCO_3 solution, water and brine, dried with MgSO_4 and evaporated to dryness. Trituration with hexane gave a solid which was collected by filtration, washed with hexane and dried to give the title compound (25.5g, 88%) as a crystalline solid: mp 98-99 °C; IR (KBr) 3119, 1610, 1590, 1510, 1452, 1393, 1296, 1067, 850; ^1H NMR (CDCl_3) δ 8.16 (1H, s), 7.69 (1H, d, J = 1.9), 7.42 (1H, d, J = 1.9); Anal. Calcd for $\text{C}_7\text{H}_3\text{Cl}_2\text{NO}$: C, 44.72; H, 1.61; N, 7.45; Cl, 37.70. Found: C, 44.84; H, 1.69; N, 7.31; Cl, 37.71.

(3S,4RS) t-Butyl N-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(5,7-dichlorobenzoxazol-2-yl)butanoate (204). Magnesium bromide was prepared by reaction of Mg (7.45g, 0.30mole) in THF (516ml) with I_2 (50mg) and 1,2-dibromoethane (26.3ml, 57.3g, 0.30mole) at reflux for 2h and then cooling to -40 °C. To the above was

- 379 -

added rapidly via cannula a solution of 2-lithio-5,7-dichlorobenzoxazole at 70 °C (prepared from 5,7-dichlorobenzoxazole (**203**, 28.9g, 0.154mole) and butyl lithium (100ml 1.52M in hexane) in THF (150ml) at -
5 70 °C). The mixture was stirred at -40 °C for 1h and then cooled to -70 °C before adding a solution of (3S) t-butyl N-(allyloxycarbonyl)-3-amino-4-oxo-butanoate (Chapman, et al., Bioorg. & Med. Chem. Lett., 2, pp. 613-618 (1992)) (20.3g, 0.078mole) in THF (160ml) at
10 less than -60 °C. The reaction was allowed to warm to ambient temperature and was stirred for 16h before quenching with ammonium chloride solution and extracting with 1:1 hexane:ethylacetate 600ml. The organic solution was washed with water and brine, dried
15 with MgSO₄ and evaporated to a syrup (52.9g). Flash chromatography (SiO₂ 250g -11 aliquots of 1:1 hexane: CH₂Cl₂ x2, CH₂Cl₂, 5% EtOAc in CH₂Cl₂, 10% EtOAc in CH₂Cl₂, 20% EtOAc in CH₂Cl₂) gave impure product 24.6g which on further chromatography (SiO₂ 1:1 hexane:ether)
20 give the title compound as a golden-brown glass (22.7g, 64%); IR (film) 3343, 2980, 1723, 1712, 1520, 1456, 1398, 1369, 1254, 1158, 993; ¹H NMR (CDCl₃) δ 7.60 (1H, m), 7.37 (1H, m), 5.72 (1H, m), 5.64 (0.5H, d), 5.10 (2.5H, m), 4.7-4.3 (4H, m), 2.9-2.6 (2H, m), 1.46 and
25 1.42 (9H combined, 2 x s). MS ES⁺ Da/e 445 (M + 1)⁺ Cl 35 62%, 447 (M + 1)⁺ Cl 37 40%, 389 100%.

- 380 -



(2*S*)-*N*-Allyloxycarbonyl-5-(1,1-dimethylethyl)glutamate (205a). To a mixture of THF (200ml) and water (100ml) containing NaHCO₃ (16.6g, 0.2mol) was added glutaric acid *t*-butyl ester (10g, 49.2mmol) and then dropwise over 20 minutes allyl chloroformate (6.8ml, 64mmol). The mixture was stirred for 2 hours, extracted with EtOAc, washed with a sat. hydrogenocarbonate solution, water and a sat. salt solution, dried and evaporated to an oil **205a** (9.5g, 67.2%); $[\alpha]_D^{20} -6^\circ$ (c 1.5, MeOH)

¹H NMR (D₆-DMSO) δ 6.10 (1H, d), 5.96-5.88 (1H, m), 5.31-5.12 (2H, m), 4.45 (2H, m), 3.90-3.84 (1H, t), 2.18 (2H, m), 1.85-1.76 (2H, m), 1.36 (9H, s).

(2*R*)-*N*-Allyloxycarbonyl-5-(1,1-dimethylethyl)glutamate (205b), was prepared by an analogous method to 205a to afford a colourless oil (6.27g, 88%); $[\alpha]_D^{20} +16^\circ$ (c 0.095, MeOH); IR (KBr) 3678, 3332, 3088, 2980, 2937, 1724, 1530, 1453, 1393, 1370, 1331, 1255, 1155, 1056, 995, 935, 845, 778, 757, 636, 583; ¹H NMR (CDCl₃) δ

- 381 -

9.24 (1H, broad s), 5.94-5.79 (1H, m), 5.58 (1H, d),
 5.33-5.17 (2H, m), 4.55 (2H, d), 4.38-4.31 (1H, m),
 2.41-1.95 (4H, m), 1.42 (9H, s); Anal. Calcd for
 $C_{13}H_{21}NO_6$: C, 54.35; H, 7.37; N, 4.88. Found: C,
 5 54.4; H, 7.5; N, 4.8.

(4S) t-Butyl N-allyloxycarbonyl-4-amino-5-hydroxypentanoate (206a). To a solution of 205a (3.6g, 12.5mmol) in THF (100ml) at 0 °C was added N-methyl morpholine (1.5ml, 13mmol) followed by isobutyl
 10 chloroformate, (1.1ml, 13mmol). After 15 minutes, this mixture was added to a suspension of $NaBH_4$ (0.95g, 25mmol) in THF (100ml) and MeOH (25ml) at -78 °C. After 2 hours at -70 °C, the mixture was quenched with acetic acid, diluted with EtOAc, washed with a sat.
 15 hydrogenocarbonate solution 3 times, water and a sat. solution of salt, dried and evaporated. Flash chromatography (2% MeOH in CH_2Cl_2) afforded 206a as a colourless oil (2.4g, 70%): $[\alpha]_D^{20}$ -10 ° (c 3.88, CH_2Cl_2); 1H NMR ($CDCl_3$) δ 5.84 (1H, m), 5.34-5.17 (3H, m), 4.56-4.53 (2H, m), 3.68-3.59 (2H, m), 2.98 (1H, m),
 20 2.40-2.30 (2H, t), 1.84-1.78 (2H, m), 1.43 (9H, s); Anal. Calcd for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.12. Found: C, 57.1; H, 8.6; N, 6.0

(4R) t-Butyl N-allyloxycarbonyl-4-amino-5-hydroxypentanoate (206b), was prepared by an analogous
 25 method to 206a which afforded the title compound as a light yellow oil (3.42g, 57%): $[\alpha]_D^{20}$ +14 (c 0.166, MeOH); IR (KBr) 3341, 3083, 2976, 2936, 2880, 1724, 1533, 1454, 1419, 1369, 1332, 1251, 1156, 1062, 997,
 30 933, 846, 777, 647; 1H NMR ($CDCl_3$) δ 5.98-5.81 (1H, m), 5.35-5.10 (3H, m), 4.55 (2H, d), 3.70-3.56 (3H, m),

- 382 -

2.50-2.47 (1H, broad s), 2.37-2.30 (2H, m), 1.89-1.74 (2H, m), 1.44 (9H, s); Anal. Calcd for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.12. Found: C, 56.9; H, 8.6; N, 5.6

5 **(4S) t-Butyl N-Allyloxycarbonyl-4-amino-5-oxopentanoate (207a)**. To a solution of DMSO (1.51g, 19.3mmol) in CH_2Cl_2 (25ml) at $-70^\circ C$ was added oxalyl chloride (1.34g, 19.3mmol). After 10 minutes at $-70^\circ C$, a solution of **(206a)** (2.4g, 8.8mmol) in CH_2Cl_2 (10ml) was
 10 added dropwise and the mixture stirred for 15 minutes at $-70^\circ C$. Diisopropylethylamine (3.4g, 26.3mmol) was added and the mixture stirred at $-25^\circ C$ for 15 minutes then diluting with EtOAc (50ml) washed with a solution of sodium hydrogen sulfate 2M, concentrated to give an
 15 oil which was used immediately without purification: 1H NMR ($CDCl_3$) δ 9.5 (1H, s), 6.0-5.5 (2H, m), 5.5-5.1 (2H, m), 4.5 (2H, m), 4.2 (1H, m), 2.4-2.10 (2H, m), 2.05 (2H, m), 1.36 (9H, s).

(4R) t-Butyl N-Allyloxycarbonyl-4-amino-5-oxopentanoate (207b), was prepared by an analogous method to **207a**
 20 which afforded an oil (2.95g, 96%) which was used without further purification in the next step: $[\alpha]_D^{20} +21^\circ$ (c 0.942, MeOH); 1H NMR ($CDCl_3$) δ 9.58 (1H, s), 6.05-5.80 (1H, m), 5.57 (1H, broad s), 5.35-5.18 (2H, m), 4.56 (2H, d), 4.34-4.24 (1H, m), 2.38-2.16 (3H, m),
 25 1.96-1.73 (1H, m), 1.43 (9H, s).

(4S) t-Butyl N-Allyloxycarbonyl-4-amino-5-oxopentanoate semicarbazone (208a). To a solution of **207a** (2.39g, 8.8mmol), in MeOH (20ml) was added sodium acetate
 30 (0.72g, 8.8mmol) and semicarbazide (0.98g, 8.8mmol)

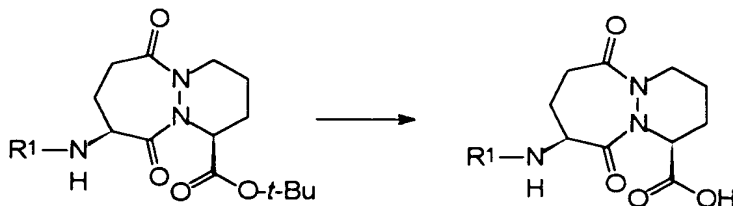
- 383 -

stirred overnight, concentrated and diluted with CH_2Cl_2 (100ml), washed with water, dried and concentrated.

Flash chromatography (2% MeOH in CH_2Cl_2) afforded **208a** (2.10g, 73%) as an oil: $[\alpha]_{\text{D}}^{20} -21$ (c 2.55°, CH_2Cl_2);

5 ^1H NMR (CDCl_3) δ 9.98 (1H, s), 7.27 (1H, d), 5.8 (1H, m), 5.5 (1H, d), 5.35-5.19 (2H, m), 4.58 (2H, m), 4.14 (1H, m), 2.37 (2H, t), 2.09 (1H, m), 2.0-1.75 (2H, m);
Anal. Calcd for $\text{C}_{14}\text{H}_{24}\text{N}_4\text{O}_5$: C, 51.21; H, 7.37; N, 17.06. Found: C, 50.2; H, 7.3; N, 16.1

10 **(4R) t-Butyl N-Allyloxycarbonyl-4-amino-5-oxopentanoate semicarbazone (208b)**, was prepared by an analogous method to **208a** which afforded a glassy oil (2.37g, 66%): $[\alpha]_{\text{D}}^{20} +30$ (c 0.26, CHCl_3); IR (KBr) 3476, 3360, 2979, 2923, 1700, 1586, 1527, 1427, 1394, 1369, 1338, 1253, 1156, 1060, 997, 929, 846, 775; ^1H NMR (CDCl_3) δ 9.87 (1H, s), 7.09 (1H, d), 6.05-5.75 (3H, m), 5.58 (1H, d), 5.32-5.16 (2H, m), 4.54 (2H, d), 4.35 (1H, m), 2.32-2.26 (2H, m), 2.15-1.55 (2H, m), 1.41 (9H, s);
15 Anal. Calcd for $\text{C}_{14}\text{H}_{24}\text{N}_4\text{O}_5$: C, 51.21; H, 7.37; N, 17.06. Found: C, 51.0; H, 7.5; N, 16.7.
20



211 (b) $\text{R}^1 = \text{MeSO}_2$
(c) $\text{R}^1 = \text{MeCO}$
(d) $\text{R}^1 = \text{PhCH}_2\text{OCO}$
(e) $\text{R}^1 = \text{PhCO}$
25 (f) $\text{R}^1 = \text{Fmoc}$

212 (b) $\text{R}^1 = \text{MeSO}_2$
(c) $\text{R}^1 = \text{MeCO}$
(d) $\text{R}^1 = \text{PhCH}_2\text{OCO}$
(e) $\text{R}^1 = \text{PhCO}$
(f) $\text{R}^1 = \text{Fmoc}$

- 384 -

(1S,9S) t-Butyl 6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxylate (211b). A solution of t-butyl 9-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (GB 2,128,984; 831mg, 2.79mmol) and diisopropylethylamine (1.22ml, 6.99mmol, 2.5 equiv) in CH₂Cl₂ (10ml) under dry nitrogen was treated with methanesulphonyl chloride (237μl, 3.07mmol 1.1 equiv). The mixture was stirred for 1h, diluted with EtOAc (75ml) and washed with saturated NaHCO₃ (50ml) and saturated aqueous sodium chloride (30ml), dried (MgSO₄) and concentrated. Flash chromatography (10-35% EtOAc in CH₂Cl₂) afforded **211b** (806mg, 77%) as a colourless solid: mp 68-70 °C; $[\alpha]_D^{23}$ -109 (c 1.09, CH₂Cl₂); IR (KBr) 3270, 2980, 2939, 1735, 1677, 1458, 1447, 1418, 1396, 1370, 1328, 1272, 1252, 1232, 1222, 1156, 1131, 991; ¹H NMR (CDCl₃) δ 6.15 (1H, d), 5.31 (1H, m), 4.65-4.11 (2H, m), 3.47 (1H, m) 2.99 (3H, s), 2.89 (1H, m), 2.72-2.51 (2H, m), 2.34 (1H, m), 2.26 (1H, m), 2.05-1.62 (4H, m), 1.47 (9H, s); Anal. Calcd for C₁₅H₂₃N₃O₆S: C, 47.97; H, 6.71; N, 11.19; S, 8.54. Found: C, 48.28; H, 6.68; N, 10.86; S, 8.28. MS (+FAB) 376 (M⁺ + 1, 66%), 320 (100).

5ch
A13

25 (1S,9S) t-Butyl 9-acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino [1,2-a]-[1,2]diazepine-1-carboxylate (211c). Acetic anhydride (307mg, 3.01mmol) was added to a stirred mixture of t-butyl 9-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (GB 2,128,984; 813.7mg, 2.74mmol), diisopropylethylamine (884mg, 6.84mmol) and CH₂Cl₂

- 385 -

Sub
A¹³

(20ml). The mixture was kept for 1h then diluted with EtOAc, washed with NaHCO₃ solution then brine, dried (MgSO₄) and concentrated to yield a colourless oil. The product was purified by flash chromatography (0.5-
5 8% MeOH/CH₂Cl₂) to afford **211c** (804mg, 71%) of colourless powder: mp 162-3 °C; $[\alpha]_D^{23}$ -109 (c 1.03, CH₂Cl₂); IR(KBr) 3358, 2974, 1733, 1693, 1668, 1528, 1462, 1431, 1406, 1371, 1278, 1271, 1250, 1233, 1217, 1154, 1124; δ ¹H NMR (CDCl₃) δ 8.32 (1H, d), 5.29-5.25
10 (1H, m), 4.98-4.85 (1H, m), 4.68-4.58 (1H, m), 3.55-3.39 (1H, m), 2.91-2.66 (2H, m), 2.39-2.18 (2H, m), 2.03 (3H, s), 1.88-1.64 (4H, m), 1.47 (9H, s); Anal. Calcd for C₁₆H₂₅N₃O₅: C, 56.62; H, 7.43; N, 12.38. Found: C, 56.62; H, 7.43; N, 12.36; MS (+ FAB) 340 (M⁺
15 + 1, 40%), 284 (100).

(1S,9S) t-Butyl 9-(benzyloxycarbonylamino)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (**211d**). Benzyl chloroformate (1.07g) was added dropwise to a stirred ice cold
20 mixture of the (1S,9S) t-butyl 9-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (GB 2,128,984; 1.55g, 5.21mmol), NaHCO₃ (0.66g, 7.82mmol), dioxan (32ml) and water (8ml). The mixture was kept at 5 °C for 15min
25 then for 2h at room temperature. The mixture was diluted with EtOAc (50ml), washed twice with sat. NaHCO₃ solution, dried (MgSO₄) and concentrated. The oily residue was purified by flash chromatography to afford **211d** (1.98g, 88%) of a colourless oil: $[\alpha]_D^{24}$ -
30 56.4 (c 1.0, CH₂Cl₂); IR(thin film) 3325, 2979, 2946, 1728, 1677, 1528, 1456, 1422, 1370, 1340, 1272, 1245, 1156, 1122, 1056, 916, 734, 699; ¹H NMR (CDCl₃) δ 7.29

- 386 -

(5H, m), 5.81-5.72 (1H, m), 5.26-5.20 (1H, m), 5.05 (2H, s), 4.69-4.51 (2H, m), 3.48-3.36 (1H, m), 2.81-2.51 (2H, m), 2.34-2.19 (2H, m), 1.90-1.54 (4H, m), 1.41 (9H, s); Anal. Calcd for $C_{22}H_{29}N_3O_6 \cdot H_2O$: C, 58.79; H, 6.92; N, 9.35. Found: C, 59.10; H, 6.57; N, 9.25; MS (ES +) 454 (M^+Na , 87%), 432 (M^++1 , 100).

(1S,9S) t-Butyl 9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxylate (211e). A solution of benzoyl chloride (1.61g, 11.47mmol) in CH_2Cl_2 (15ml) was added dropwise to a stirred ice cold mixture of (1S,9S) t-butyl 9-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (GB 2,128,984; 3.1g, 10.43mmol), dry CH_2Cl_2 (20ml) and diisopropylethylamine (4.54ml, 26.06mmol). The mixture was kept cold for 1h then left at room temperature for 0.5h. The mixture was diluted with CH_2Cl_2 , washed twice with brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (0-5% methanol in CH_2Cl_2) to afford **211e** (4.0g, 96%) of a colourless glass: mp 74-76 °C; $[\alpha]_D^{30}$ -75.0 ° (c 0.12, CH_2Cl_2). IR (KBr) 3350, 2979, 2938, 1736, 1677, 1662, 1536, 1422, 1276, 1250, 1155; 1H NMR ($CDCl_3$) δ 8.72 (2H, m), 7.53-7.40 (3H, m), 7.07 (1H, d, J = 7.2), 5.30 (1H, dd, J = 3.0, 5.8), 5.12 (1H, m), 4.66 (1H, m), 3.51 (1H, m), 2.90 (2H, m), 2.38 (1H, dd, J 13.2, 6.8), 2.25 (1H, m), 1.9 (2H, m), 1.70 (1H, m). Anal. Calcd for $C_{21}H_{27}N_3O_5 \cdot 0.5H_2O$: C, 61.45; H, 6.88; N, 10.24. Found C, 61.69; H, 6.71; N, 10.18.

(1S,9S) t-Butyl 6,10-dioxo-9-(fluoren-9-ylmethoxy-carbonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-

- 387 -

pyridazino[1,2-a][1,2]-diazepine-1-carboxylate (211f), was prepared in a similar manner to 211e, except 9-fluorenylmethylchloroformate was used instead of benzoylchloride to give a white glassy solid 211f

- 5 (2.14g, 89%): mp 190-192 °C; $[\alpha]_D^{25}$ -81.5 ° (c 0.1, CH₂Cl₂). IR (KBr) 3335, 2977, 1731, 1678, 1450, 1421, 1246, 1156, 742; ¹H NMR (CDCl₃) δ 7.60 (2H, m), 7.57 (2H, m), 7.50-7.26 (4H, m), 5.60 (1H, d, J = 7.8), 5.28 (1H, m), 4.67 (2H, m), 4.38 (2H, m), 4.23 (1H, m),
10 3.59-3.41 (1H, m), 2.92-2.65 (2H, m), 2.41-2.21 (2H, m), 1.95-1.58 (4H, m), 1.47 (9H, s). MS(ES⁻, m/z) 520 (M⁺ + 1, 97%), 179 (100%).

(1S,9S) 6,10-Dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-

- 15 [1,2-a][1,2]diazepine-1-carboxylic acid (212b), was synthesized by the same method as compound 212e (635mg, 85%) as a colourless powder: mp 209-12 °C; $[\alpha]_D^{24}$ -132 (c 0.12, MeOH); IR (KBr) 3308, 2940, 1717, 1707, 1699, 1619, 1469, 1456, 1442, 1417, 1391, 1348, 1339, 1330,
20 1310, 1271, 1247, 1222, 1175, 1152, 1133, 993, 976; ¹H NMR (CD₃OD) δ 5.35 (1H, m), 4.58-4.48 (1H, m), 4.46-4.36 (1H, m), 3.60-3.42 (1H, m), 3.01-2.87 (1H, m), 2.95 (3H, s), 2.55-2.39 (1H, m), 2.32-2.20 (2H, m), 2.09-1.89 (2H, m), 1.78-1.62 (2H, m); Anal. Calcd for
25 C₁₁H₁₇N₃O₆S: C, 41.37; H, 5.37; N, 13.16; S, 10.04. Found: C, 41.59; H, 5.32; N, 12.75; S, 9.76; MS(ES⁻). Accurate Mass calculated for C₁₁H₁₈N₃O₆S (MH⁺): 320.0916. Found: 320.0943.

- (1S,9S) 9-Acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-
30 octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid (212c), was prepared from 211e the same

- 388 -

method as compound **212e** as a white glassy solid (595mg, 77%): mp >250 °C; $[\alpha]_D^{24}$ -153 (c 0.10, MeOH); IR (KBr) 3280, 2942, 1742, 1697, 1675, 1650, 1616, 1548, 1470, 1443, 1281, 1249, 1202, 1187, 1171; ^1H NMR (CD_3OD) δ 5.35-5.31 (1H, m), 4.81-4.71 (1H, m), 4.61-4.46 (1H, m), 3.59-3.44 (2H, m), 3.11-2.94 (1H, m), 2.58-2.39 (1H, m), 2.36-2.19 (2H, m), 2.11-1.83 (3H, m), 1.99 (3H, s), 1.78-1.56 (2H, m); Anal. Calcd for $\text{C}_{12}\text{H}_{17}\text{N}_3\text{O}_5$: C, 50.88; H, 6.05; N, 14.83. Found: C, 50.82; H, 6.02; N, 14.58; MS (ES -) 282 (M-1, 100%): Accurate Mass calculated for $\text{C}_{12}\text{H}_{18}\text{N}_3\text{O}_5$ (MH^+): 284.1246. Found: 284.1258.

(1*S*,9*S*) 9-Benzylloxycarbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-*a*][1,2]diazepine-1-carboxylic acid (**212d**), was prepared from **211d** by the same method as compound **212e** as colourless crystals (170mg, 97%): mp 60-100 °C; $[\alpha]_D^{22}$ -103 (c 0.10, MeOH); IR (KBr) 3341, 2947, 1728, 1675, 1531, 1456, 1422, 1339, 1272, 1248, 1221, 1174, 1122, 1056, 982, 699; ^1H NMR (CDCl_3) δ 7.35 (5H, s), 5.65 (1H, d), 5.48-5.40 (1H, m), 5.10 (2H, s), 4.76-4.57 (2H, m), 3.49-3.30 (2H, m), 2.92-2.59 (2H, m), 2.40-2.27 (2H, m), 1.97-1.67 (4H, m); MS (ES -) 374 (M - 1, 100%). Accurate mass calculated for $\text{C}_{18}\text{H}_{22}\text{N}_3\text{O}_6$ (MH^+): 376.1509. Found: 376.1483. Accurate mass calculated for $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_6\text{Na}$ (MNa^+): 398.1328. Found: 398.1315.

(1*S*,9*S*) 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]-diazepine-1-carboxylic acid (**212e**). TFA (20ml) was added to an ice cold stirred solution of the t-butyl ester **211e** (4.15g,

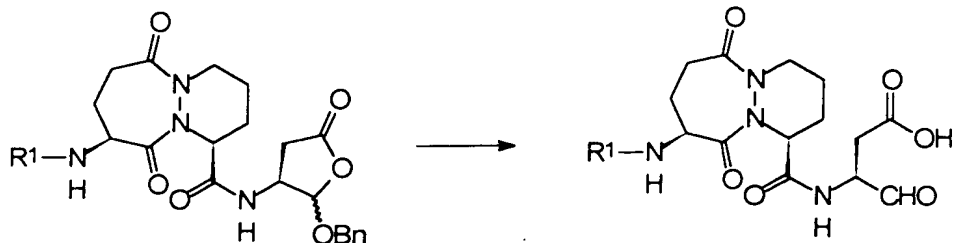
- 389 -

10.34mmol) in dry CH_2Cl_2 (20ml). The mixture was kept cold for 1.5h then left for 2.5h at rt, concentrated. TFA was removed by repeated concentrations of CH_2Cl_2 /ether and ether solutions of the residue.

- 5 Finally trituration of the residue with ether afforded **212e** 3.05g (85%) of a white glassy solid: mp 118-126 °C; $[\alpha]_{\text{D}}^{24} -70.5^\circ$ (c 0.1, CH_2Cl_2). IR (KBr) 3361, 2943, 1737, 1659, 1537, 1426, 1220, 1174; ^1H NMR (CDCl_3) δ 7.80 (2H, m), 7.54-7.33 (4H, m), 8.83 (brs),
10 5.44 (1H, m), 5.26-5.13 (1H, m), 4.66 (1H, m), 3.59-3.41 (1H, m), 2.97, 2.76 (2H, 2m), 2.36 (2H, m), 1.98 (2H, m), 1.75 (2H, m). MS(ES^- , m/z) 344 ($\text{M} - 1$, 100%).

- (1*S*,9*S*) 6,10-Dioxo-9(fluoren-9-ylmethyloxycarbonylamino)-1,2,3,4,7,8,9,10-octahydro-
15 6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxylic acid (**212f**), was prepared from **211f** in 96% yield by the same method as for **212e**: mp 120-126 °C; $[\alpha]_{\text{D}}^{25} -72.5^\circ$ (c 0.1, CH_2Cl_2). IR (KBr) 3406, 2950, 1725, 1670, 1526, 1449, 1421, 1272, 1248, 1223, 1175, 761, 741;
20 ^1H NMR (CDCl_3) δ 7.76 (2H, m), 7.62-7.26 (4H, m), 6.07, 5.76 (2H, brs, d, d, $J = 2.9$), 5.46, 5.36 (1H, 2m), 4.79-4.54 (2H, m), 4.77 (2H, m), 4.21 (1H, m), 3.41 (1H, m), 2.89 (1H, m), 2.69 (1H, m), 2.35 (2H, m), 1.98, 1.73 (4H, 2m). MS(ES^- , m/z) 462 ($\text{M}^+ - 1$, 50%),
25 240 (100%).

- 390 -



(213) (c) $R^1 = \text{MeCO}$
 (e) $R^1 = \text{PhCO}$

(214) (c) $R^1 = \text{MeCO}$
 (e) $R^1 = \text{PhCO}$

[2*RS*,3*S*(1*S*,9*S*)] *N*-(2-Benzoyloxy-5-oxotetrahydrofuran-3-yl)-9-(acetylamino)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide (213*c*), was synthesized from 212*c* by the same method as compound 213*e* to afford a mixture of diastereomers (193mg, 36%) as colourless crystals: IR (KBr) 3272, 1799, 1701, 1682, 1650, 1555, 1424, 1412, 1278, 1258, 1221, 1122, 937; ^1H NMR (CDCl_3) δ 7.41-7.28 (5*H*, m), 6.52 (0.5*H*, d), 6.38 (0.5*H*, d), 6.22 (0.5*H*, d), 5.57 (0.5*H*, d), 5.36 (0.5*H*, s) 5.10-5.05 (1*H*, m), 5.00-4.45 (5.5*H*, m), 3.19-2.84 (3*H*, m), 2.72-2.56 (1*H*, m), 2.51-2.25 (2*H*, m), 2.02 (3*H*, s), 1.98-1.70 (3*H*, m), 1.66-1.56 (3*H*, m); Anal. Calcd for $\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_7$: C, 58.47; H, 5.97; N, 11.86. Found: C, 58.37; H, 6.09; N, 11.47. MS (ES $-$) 471 (*M*-1, 100%). Accurate mass calculated for $\text{C}_{23}\text{H}_{29}\text{N}_4\text{O}_7$ (MH^+): 473.2036. Found: 473.2012. Accurate mass calculated for $\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_7\text{Na}$ (MNa^+): 495.1856. Found: 495.1853.

[1*S*,9*S*(2*RS*,3*S*)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-*N*-(2-benzoyloxy-5-oxotetrahydrofuran-3-yl)-6*H*-pyridazino[1,2-*a*][1,2]-diazepine-1-carboxamide (213*e*). Tributyltin hydride (2.2ml, 8.18mmol) was added dropwise to a solution of

- 391 -

acid **212e** (1.95g, 5.6mmol), (3*S*, 2*RS*) 3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran (Chapman, Bioorg. & Med. Chem. Lett., 2, pp. 615-618 (1992); 1.80g, 6.16mmol) and (Ph₃P)₂PdCl₂ (50mg) in dry CH₂Cl₂ (36ml), with stirring, under dry nitrogen. After 5 min 1-hydroxybenzotriazole (1.51g, 11.2mmol 6.72mmol) was added followed after cooling (ice/H₂O) by ethyldimethylaminopropyl carbodiimide hydrochloride (1.29g, 6.72mmol). After 5 mins the cooling bath was removed and the mixture was kept at room temperature for 4h, diluted with EtOAc, washed with 1M HCl, brine, sat. aq. NaHCO₃ and brine, dried (MgSO₄) and concentrated. Flash chromatography (silica gel, 0-90% EtOAc in CH₂Cl₂) gave the product as a white solid (2.34g, 78%): IR (KBr) 3499, 1792, 1658, 1536, 1421, 1279, 1257, 1123, 977, 699; ¹H NMR (CDCl₃) δ 7.81 (2H, m), 7.54-7.34 (8H, m), 7.1, 6.97, 6.89, 6.48 (2H, m, d, *J* 7.7, d, *J* = 7.5, d, *J* = 7.6), 5.57, 5.28 (1H, d, *J* = 5.2, s), 5.23-5.07 (2H, m), 4.93-4.42, 3.22-2.70, 2.51-2.26, 2.08-1.69, 1.22 (15H, 5m). Anal. Calcd for C₂₈H₃₀N₄O₇ 0.5H₂O: C, 61.87; H, 5.75; N, 10.32. Found C, 62.02; H, 5.65; N, 10.25.

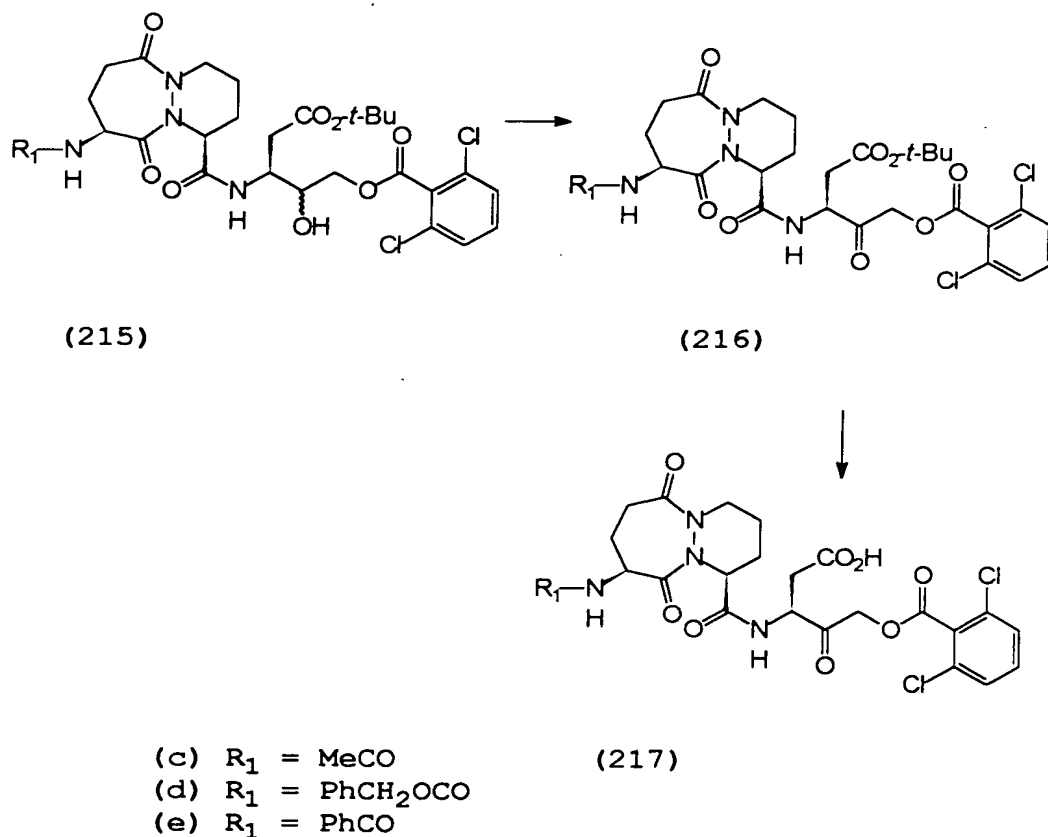
[3*S*(1*S*,9*S*)] 3-(9-Acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-*a*][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (**214c**), was synthesized from **213c** by a method similar to the method used to synthesize **214e** from **213e** to provide colourless crystals (140mg, 99%): mp 90-180 °C; [α]_D²² -114 (c 0.10, MeOH); IR (KBr) 3334, 3070, 2946, 1787, 1658, 1543, 1422, 1277, 1258; ¹H NMR (d⁶-DMSO) δ 8.66 (1H, m), 8.18 (1H, d), 6.76 (1H, s), 5.08 (1H, m), 4.68 (1H, m), 4.30 (1H, m), 2.92-2.70 (2H, m),

- 392 -

2.27-2.06 (3H, m), 1.95-1.72 (4H, m), 1.85 (3H, s),
1.58 (2H, m); MS(ES -) 381 (M-1, 100%); Accurate mass
calculated for $C_{16}H_{23}N_4O_7$ (MH^+): 383.1567. Found:
383.1548.

- 5 [3*S*(1*S*,9*S*)] 3-(9-Benzoylamino-6,10-dioxo-
1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]-
diazepine-1-carboxamido)-4-oxobutanoic acid (214e). A
mixture of 213e (2.29g, 4.28mmol), 10% palladium on
carbon (1.8g) and MeOH (160ml) was stirred under H_2 at
10 atmospheric pressure for 6.3h. After filtering and
concentrating the hydrogenation was repeated with fresh
catalyst (1.8g) for 5h. After filtering and
concentrating the residue was triturated with diethyl
ether, filtered and washed well with ether to give 214e
15 as a white solid (1.67g, 88%): mp 143-147 °C; $[\alpha]_D^{23}$ -
125 ° (c 0.2, CH_3OH). IR (KBr) 3391, 1657, 1651, 1538,
1421, 1280, 1258; 1H NMR (CD_3OD) δ 7.90 (2H, m), 7.63-
7.46 (3H, m), 5.25 (1H, m), 5.08-4.85 (1H, m), 4.68-
4.53 (2H, m), 4.33-4.24 (1H, m), 3.62-3.44, 3.22-3.11,
20 2.75-2.21, 2.15-1.92, 1.73-1.66 (11H, 5m). Anal. Calcd
for $C_{21}H_{24}N_4O_7 \cdot H_2O$: C, 54.54; H, 5.67; N, 12.11. Found
C, 54.48; H, 5.63; N, 11.92.

- 393 -



- 5 [3*S*,4*RS*(1*S*,9*S*)] *t*-Butyl 3-[9-acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino-
- [1,2-*a*][1,2]diazepine-1-carboxamido)-5-(2,6-
- dichlorobenzoyloxy)-4-hydroxypentanoate (215c), was
- synthesized from 214c by the same method as compound
- 10 215e, to afford a mixture of diastereomers as a white
- glassy solid (398mg, 84%): IR (KBr) 3338, 2977, 1738,
- 1658, 1562, 1541, 1433, 1368, 1277, 1150; ^1H NMR
- (CDCl_3) δ 7.36-7.32 (3H, m), 6.91 (1H, d), 6.30 (1H,
- d), 5.15-5.09 (1H, m) 5.01-4.88 (1H, m), 4.61-4.44 (2H,
- 15 m), 4.37-4.08 (3H, m), 3.32-3.18 (1H, m), 3.04-2.89
- (1H, m), 2.82-2.51 (4H, m), 2.39-2.29 (1H, m), 2.08-
- 1.64 (4H, m) 2.02 (3H, s); Anal. Calcd for

- 394 -

$C_{28}H_{34}N_4Cl_2O_9$: C, 52.26; H, 5.64; N, 8.71. Found: C, 52.44; H, 5.87; N, 8.16. MS (ES -) 645/3/1 (M-1, 26%), 189 (81), 134 (100). Accurate mass calculated for $C_{28}H_{37}N_4Cl_2O_9$ (MH^+): 643.1938. Found: 643.1924.
 5 Accurate mass calculated for $C_{28}H_{36}N_4Cl_2O_9Na$ (MNa^+) 665.1757. Found: 665.1756.

[3*S*,4*RS*(1*S*,9*S*)] *t*-Butyl 3-(9-benzyloxycarbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-5-(2,6-dichlorobenzyloxy)-4-hydroxypentanoate (215*d*), was
 10 synthesized from 214*d* by the same method as compound 215*e* to afford a mixture of diastereomers (657mg, 70%) as a glassy white solid: IR (KBr) 3420, 3361, 2975, 2931, 1716, 1658, 1529, 1434, 1367, 1348, 1250, 1157,
 15 1083, 1055; 1H NMR ($CDCl_3$) δ 7.32 (8*H*, m), 7.14 (1*H*, d), 5.81 (1*H*, d), 5.15 (1*H*, m), 5.07 (2*H*, s), 4.74-4.65 (1*H*, m), 4.58-4.22 (4*H*, m), 4.15-4.06 (1*H*, m), 3.72 (1*H*, m), 3.32-3.21 (1*H*, m), 3.04-2.94 (1*H*, m), 2.69-2.52 (3*H*, m), 2.33-2.27 (1*H*, m), 1.95-1.59 (4*H*, m),
 20 1.28 (9*H*, s); Anal. Calcd for $C_{34}H_{40}N_4Cl_2O_{10} \cdot 0.5 H_2O$: C, 54.70; H, 5.54; N, 7.50. Found: C, 54.98; H, 5.59; N, 7.24. MS (ES -) 737/5/3 (M-1, 22%), 193/1/89 (100). Accurate mass calculated for $C_{34}H_{41}N_4Cl_2O_{10}$ (MH^+) 735.2120. Found: 735.2181.

25 [3*S*,4*RS*(1*S*,9*S*)] *t*-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino-[1,2-*a*][1,2]diazepine-1-carboxamido)-5-(2,6-dichlorobenzyloxy)-4-hydroxypentanoate (215*e*),
 Tributyltin hydride (4.6ml; 11.4mmol) was added
 30 dropwise to a stirred mixture of (3*S*,4*RS*) *t*-Butyl (N-allyloxycarbonyl)-3-amino-5-(2,6-dichlorobenzoyloxy)-4-

- 395 -

hydroxypentanoate (prepared by a method similar to the method described in Revesz et al., Tetrahedron. Lett., 35, pp. 9693-9696 (1994)) (2.64g; 5.7mmol), (Ph₃P)₂PdCl₂ (50mg), CH₂Cl₂ (100ml) and DMF (20ml) at room temperature. The mixture was stirred for a further 10min was then 1-hydroxybenzotriazole (1.54g, 11.4mmol) was added. The mixture was cooled to 0 °C then ethyldimethylaminopropyl carbodiimide hydrochloride (1.31g; 6.84mmol) added. The mixture was kept at this temperature for 15min then at room temperature for 17h. The mixture was diluted with EtOAc (300ml), washed with 1M HCl (2x100ml), sat. aq. NaHCO₃ (3x100ml) and brine (2x100ml), dried (MgSO₄) and concentrated. The residue was purified by flash chromatography (2-5% (MeOH/CH₂Cl₂) to afford 3.24g (81%) of **215e** as a glassy solid: mp 106-110 °C; IR (KBr) 3354, 1737, 1659, 1531, 1433, 1276, 1150; ¹H NMR (CDCl₃) δ 7.80 (2H, dd, *J* = 7.9 and 1.5), 7.75-7.26 (6H, m), 7.14-6.76 (2H, m), 5.30-5.02 (2H, m), 4.63-4.11 (5H, m), 3.44-3.26 (2H, m), 3.10-2.30 (5H, m), 2.10-1.60 (5H, m), 1.44 (9H, s); Anal. Calcd for C₃₃H₃₈Cl₂N₄O₉ · 0.75H₂O: C, 55.12; H, 5.54; N, 7.79; Cl, 9.86. Found: C, 55.04; H, 5.34; N, 7.80; Cl, 10.24. MS (ES +) 709/7/5 (*M* + 1), 378 (59), 324 (64), 322 (100).

[3S(1S,9S)] t-Butyl 3-(9-acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoate (216c), was synthesized from **215c** by the same method as compound **216e** as a glassy white solid (300mg, 83%): mp 80-125 °C; [α]_D²³ -89.1 (c 1.08, CH₂Cl₂); IR (KBr) 3356, 2979, 2935, 1740, 1659, 1532,

- 396 -

1434, 1369, 1276, 1260, 1151; ^1H NMR (CDCl_3) δ 7.39-7.32 (3H, m), 7.13 (1H, d), 6.34 (1H, d), 5.22-5.17 (1H, m), 5.11 (1H, d), 5.04 (1H, d), 4.99-4.88 (2H, m), 4.64-4.52 (1H, m), 3.29-3.11 (1H, m), 3.05-2.67 (4H, m), 2.39-2.29 (1H, m), 2.02 (3H, s), 1.98-1.75 (4H, m), 1.46 (9H, s); Anal. Calcd for $\text{C}_{28}\text{H}_{34}\text{N}_4\text{Cl}_2\text{O}_9$: C, 52.42; H, 5.34; N, 8.73. Found: C, 52.53; H, 5.70; N, 7.85. MS (ES $-$) 643/41/39 (M-1, 100%). Accurate mass calculated for $\text{C}_{28}\text{H}_{35}\text{N}_4\text{Cl}_2\text{O}_9$ (MH^+): 641.1781. Found: 641.1735. Accurate mass calculated for $\text{C}_{28}\text{H}_{34}\text{N}_4\text{Cl}_2\text{O}_9\text{Na}$ (Mna^+): 663.1601. Found: 663.1542.

[3S(1S,9S)] t-Butyl 3-(9-benzyloxycarbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoate (216d), was synthesized from 215d by the same method as compound 216e to afford 216d as a white glassy solid (688mg, 68%): mp 90-170 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{25}$ -83.4 (c 1.01, CH_2Cl_2); IR (KBr) 3338, 2933, 1736, 1670, 1525, 1433, 1417, 1368, 1258, 1151, 1056, 1031; ^1H NMR (CDCl_3) δ 7.33 (8H, m), 7.18 (1H, d), 5.65 (1H, d), 5.19 (1H, m), 5.09 (2H, s), 4.98-4.86 (1H, m), 4.82-4.49 (2H, d), 3.30-3.07 (1H, m), 3.05-2.59 (4H, m), 2.42-2.27 (1H, m), 2.18-1.59 (5H, m), 1.42 (9H, s); MS (ES $-$) 737/5/3 (M, 13%), 185 (100).

[3S(1S,9S)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoate (216e). Dess-Martin reagent (3.82g; 9.0mmol) was added to a stirred solution of the alcohol 215e (3.17g; 4.5mmol) in

- 397 -

CH₂Cl₂ (100ml). The mixture was stirred for 1h, diluted with EtOAc (300ml), then washed with a 1:1 mixture of sat. Na₂S₂O₃ and sat. NaHCO₃ (100ml) followed by brine (100ml). The mixture was dried (MgSO₄) then

5 concentrated. The residue was purified by flash chromatography to afford 2.2g (70%) of **216e** as a colourless solid: mp 102-107 °C; $[\alpha]_D^{32}$ -82.5 (c 0.1, CH₂Cl₂); IR (KBr) 3374, 2937, 1739, 1661, 1525, 1433, 1275, 1260, 1152; ¹H NMR (CDCl₃) δ 7.85-7.78 (2H, m),

10 7.57-7.32 (6H, m), 7.09 (1H, d, *J* = 7.9), 7.01 (1H, d, *J* 7.3), 5.25-5.16 (1H, m), 5.16-5.05 (1H, m), 5.15 (1H, d), 5.03 (1H, d), 4.99-4.90 (1H, m), 4.68-4.54 (1H, m), 3.31-3.17 (1H, m), 3.17-2.72 (4H, m), 2.45-2.35 (1H, m), 2.30-1.66 (5H, m), 1.44 (9H, s); Anal. Calcd for

15 C₃₃H₃₆Cl₂N₄O₉ · 0.5H₂O: C, 55.62; H, 5.23; N, 7.86; Cl, 9.95. Found: C, 55.79; H, 5.15; N, 7.80; Cl 9.81. MS (ES +) 729/7/5 (M + Na), 707/5/3 (M + 1), 163 (100%).

[3*S*(1*S*,9*S*)] 3-(9-Acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-

20 [1,2-*a*][1,2]diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoic acid (**217c**), was synthesized from **216c** by the same method as compound **217e** as a glassy white solid (166mg, 66%): mp

85-175 °C; $[\alpha]_D^{25}$ -156 (c 0.13, MeOH); IR (KBr) 3373, 2929, 1742, 1659, 1562, 1533, 1433, 1412, 1274, 1266,

25 1223, 1197, 1145, 1138; ¹H NMR (CD₃OD) δ 7.38 (3H, s), 5.14-5.03 (1H, m), 4.49-4.32 (2H, m), 3.50-3.27 (1H, m), 3.11-2.92 (1H, m), 2.84-2.62 (2H, m), 2.46-2.11 (2H, m), 2.05-1.46 (5H, m), 1.92 (3H, s); Anal. Calcd

30 for C₂₄H₂₆N₄Cl₂O₉ · H₂O: C, 47.77; H, 4.68; N, 9.29. Found: C, 47.75; N, 4.59; N, 9.07. MS (ES +) 627/5/3 (M+K, 21%), 611/9/7 (M+Na, 87), 589/7/5 (M⁺ +1, 71),

- 398 -

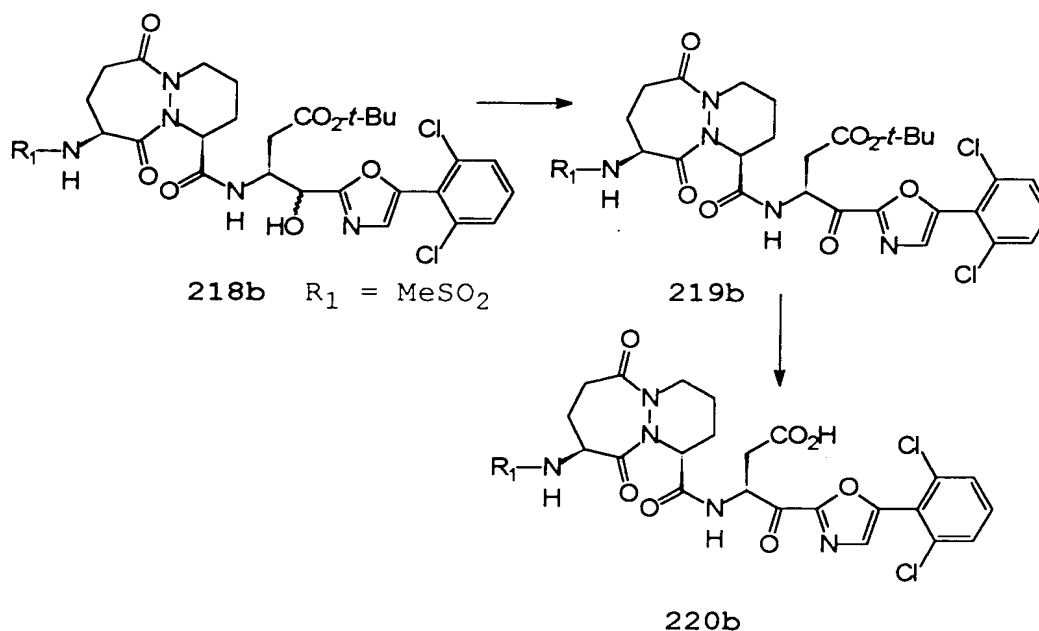
266 (100); Accurate mass calculated for $C_{24}H_{27}N_4Cl_2O_9$ (MH^+): 585.1155. Found: 585.1134.

[3S(1S,9S)] 3-(9-Benzoyloxycarbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoic acid (217d), was synthesized from 216d by the same method as compound 217e to afford 217d as a white glassy solid (310mg, 96%): mp 85-110 °C; $[\alpha]_D^{24}$ -85.9 (c 0.13, MeOH); IR (KBr) 3351, 2945, 1738, 1669, 1524, 1433, 1258, 1147, 1057; 1H NMR (CD_3OD) δ 7.56 (4H, m), 7.45 (5H, m), 5.32 (2H, m), 5.20 (2H, s), 4.76-4.48 (3H, m), 3.65-3.38 (3H, m), 3.27-3.09 (2H, m), 3.03-2.89 (2H, m), 2.65-2.24 (3H, m), 2.19-1.62 (5H, m); MS (ES -) 679/7/5 (M-1, 100%); Accurate mass calculated for $C_{30}H_{31}N_4Cl_2O_{10}$ (MH^+): 677.1417. Found: 677.1430.

[3S(1S,9S)] 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoic acid (217e), TFA (25ml) was added dropwise to an ice cold stirred solution of the ester 216e (2.11g, 3.0mmol). The mixture was stirred at 0 °C for 20min then at room temperature for 1h. The mixture was evaporated to dryness then coevaporated with ether three times. Addition of dry ether (50 ml) and filtration afforded 1.9g (98%) of 217e as a colourless solid: mp 126-130 °C; $[\alpha]_D^{30}$ -122.0 (c 0.1, MeOH); IR (KBr) 3322, 1740, 1658, 1651, 1532, 1433, 1277, 1150; 1H NMR (D_6 -DMSO) δ 8.87 (1H, d, J = 7.4), 8.61 (1H, d, J = 7.8), 7.92-7.86 (2H, m), 7.65-7.43 (6H, m), 5.25-5.12 (3H, m), 4.94-4.60 (2H, m), 4.44-4.22 (1H, m),

- 399 -

3.43-3.10 (1H, m), 3.00-2.52 (3H, m), 2.45-2.10 (3H, m), 2.10-1.75 (2H, m), 1.75-1.50 (2H, m); Anal. Calcd for $C_{29}H_{28}Cl_2N_4O_9 \cdot 1H_2O$: C, 52.34; H, 4.54; N, 8.42; Cl, 10.66. Found: C, 52.02; H, 4.36; N, 8.12; Cl, 10.36. MS (ES $-$) 649/7/5 ($M - 1$), 411 (100%).



[3*S*,4*RS*(1*S*,9*S*)] *t*-Butyl 4-[5-(2,6-dichlorophenyl)-oxazol-2-yl]-3-(6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino-[1,2-*a*][1,2]diazepine-1-carboxamido)-4-hydroxybutanoate (218b), was prepared from the acid 212b and 99 in an analogous way to compound 215e to afford a mixture of diastereomers (865mg, 80%) as a colourless solid: IR (KBr) 3298, 2974, 1723, 1659, 1544, 1518, 1430, 1394, 1370, 1328, 1273, 1256, 1156, 1134; 1H NMR ($CDCl_3$) δ 7.45-7.28 (4H, m), 7.26-7.15 (2H, m), 5.26-5.10 (2H, m), 4.80-4.67 (1H, m), 4.59-4.42 (2H, m), 3.32-3.17 (1H, m), 2.96 (3H, 2xs), 2.93-2.79 (1H, m), 2.71-2.53

- 400 -

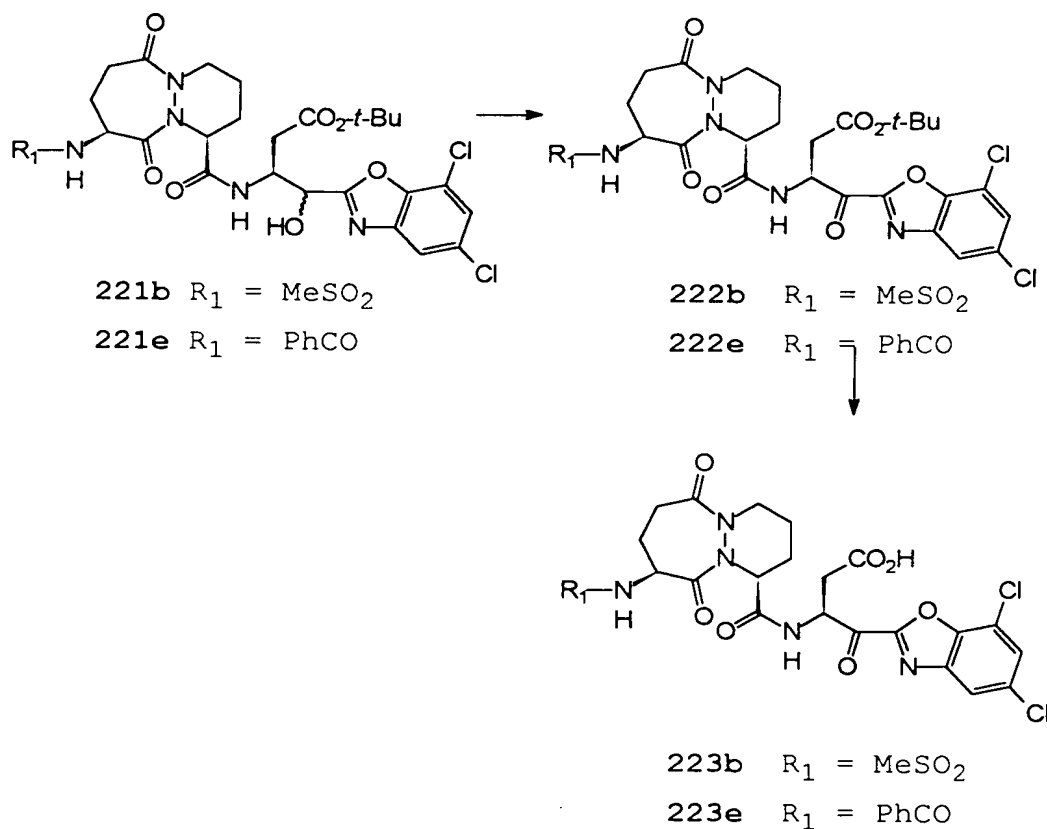
(4H, m), 2.38-2.28 (1H, m), 2.07-1.81 (4H, m); Anal. Calcd for $C_{28}H_{35}N_5Cl_2O_9S \cdot 0.5 H_2O$: C, 48.21; H, 5.20; N, 10.03. Found: C, 48.35; H, 5.26; N, 9.48. MS (ES +) 714/2/0 ($M + Na$, 25%), 692/90/88 ($M^+ + 1$, 51),
 5 636/4/2 (38), 246 (100). Accurate mass calculated for $C_{28}H_{36}N_5Cl_2O_9S$ (MH^+): 688.1611. Found: 688.1615.

[3S(1S,9S)]t-Butyl 4-[5-(2,6-dichlorophenyl)-oxazol-2-yl]-3-(6,10-dioxo-9-methylsulphonylamino-
 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]di
 10 azepine-1-carboxamido)-4-oxobutanoate (219b), was prepared from 218b in an analogous way to compound 216e as an off-white powder (675mg, 81%): mp 100-200 °C; $[\alpha]_D^{24}$ -84.9 (c 1.01, CH_2Cl_2); IR (KBr) 3336, 2978, 2936, 1719, 1674, 1510, 1433, 1421, 1369, 1329, 1274,
 15 1257, 1155, 991, 789; 1H NMR ($CDCl_3$) δ 7.47-7.38 (4H, m), 7.24 (1H, d), 5.61-5.53 (1H, m), 5.48 (1H, d), 5.38-5.30 (1H, m), 4.67-4.45 (2H, m), 3.48-3.18 (2H, m), 3.04-2.90 (2H, m), 2.97 (3H, s), 2.69-2.54 (1H, m), 2.42-2.32 (1H, m), 2.22-2.15 (1H, m), 2.07-1.93 (3H,
 20 m), 1.71-1.65 (2H, m), 1.38 (9H, s); Anal. Calcd for $C_{28}H_{33}N_3Cl_2O_9S$: C, 48.98; H, 4.84; N, 10.20; S, 4.67. Found: C, 48.73; H, 4.95; N, 9.65; S, 4.54. MS (ES +) 692/90/88 ($M^+ + 1$, 100%), 636/4/2 (71). Accurate mass calculated for $C_{28}H_{34}N_5Cl_2O_9S$ (MH^+): 686.1454. Found:
 25 686.1474.

[3S(1S,9S)] 4-[5-(2,6-Dichlorophenyl)oxazol-2-yl]-3-(6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (220b), was prepared
 30 from 219b in an analogous way to compound 217e as a pale cream powder (396mg, 87%): mp 100-200 °C; $[\alpha]_D^{27}$ -

- 401 -

129 (c 0.12, MeOH); IR (KBr) 3310, 3153, 1713, 1667, 1557, 1510, 1432, 1421, 1329, 1273, 1258, 1221, 1193, 1153, 1134, 992, 789; ^1H NMR (d^6 DMSO) δ 7.88 (1H, s), 7.81-7.60 (4H, m), 5.49-5.28 (1H, m), 5.24-5.14 (1H, m), 4.46-4.22 (2H, m), 3.30-3.03 (2H, m), 2.97-2.76 (3H, m), 2.96 (3H, s), 2.46-2.24 (1H, m), 2.16-2.05 (1H, m), 2.03-1.78 (3H, m), 1.68-1.46 (2H, m); MS (ES-) 632/30/28 (M - 1, 68%), 149/7/5 (100). Accurate mass calculated for $\text{C}_{24}\text{H}_{26}\text{N}_5\text{Cl}_2\text{O}_9\text{S}$ (MH^+): 630.0828. Found: 630.0852.



15 [3*S*,4*RS*(1*S*,9*S*)] *t*-Butyl 4-(5,7-dichlorobenzoxazol-2-yl)-3-(6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino-

- 402 -

[1,2-a][1,2]diazepine-1-carboxamido)-4-hydroxybutanoate (221b), was prepared from the acid 212b and (3S,4RS) t-butyl N-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(5,7-dichlorobenzoxazol-2-yl)butanoate (204) by an analogous
 5 method as that used for compound 215e to afford a mixture of diastereomers (460mg, 70%) as a glass: IR (film) 3325, 1725, 1664, 1453, 1399, 1373, 1327, 1274, 1256, 1155; ¹H NMR (CDCl₃) δ 7.57 (1H, m), 7.36 (2H, m), 6.06 (1H, t), 5.29 (2H, m), 4.79 (1H, m), 4.47 (1H,
 10 m), 3.23 (1H, m), 2.97 and 2.94 (3H combined, 2 x s), 2.9-2.4 (4H, m), 2.30 (1H, m), 1.96 (4H, m), 1.41 and 1.37 (9H combined, 2 x s). MS ES Da/e 660 (M - 1)⁻ Cl³⁵ 100%, 662 (M - 1)⁻ Cl³⁷.

[3S,4RS(1S,9S)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-
 15 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-4-(5,7-dichlorobenzoxazol-2-yl)-4-hydroxybutanoate (221e), was prepared from the acid (212e) and (3S,4RS) t-butyl N-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(5,7-dichlorobenzoxazol-2-yl)butanoate (204) by an analogous
 20 method as that used for compound 215e to afford a mixture of diastereomers (613mg, 87%) as a glass: IR (film) 3328, 1729, 1660, 1534, 1454, 1422, 1399, 1276, 1254, 1155; ¹H NMR (CDCl₃) δ 7.80 (2H, d), 7.60-7.35 (5H, m), 7.05 (2H, m), 5.13 (3H, m), 4.74 (1H, m), 4.51 (1H, m), 3.25 (1H, m), 3.1-2.6 (5H, m), 2.33 (1H, m), 2.1-1.5 (5H, m), 1.43 and 1.41 (9H combined, 2 x s). MS ES⁺ Da/e 688 (M + 1)⁺ Cl³⁵ 55%, 690 (M + 1)⁺ Cl³⁷ 35%, 328 100%.

30 [3S(1S,9S)]t-Butyl 4-(5,7-dichlorobenzoxazol-2-yl)-3-(6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-

- 403 -

octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoate (222b), was prepared from 221b by an analogous method as that used for compound 216e to afford a colourless glass (371mg, 86%): $[\alpha]_D^{26}$ -81.0 (c 0.1, CH₂Cl₂); IR (KBr) 3324, 2979, 2936, 1726, 1664, 1394, 1370, 1328, 1155, 991; ¹H NMR (CDCl₃) δ 7.78 (1H, d), 7.57 (2H, m), 5.87 (1H, d), 5.69 (1H, m), 5.47 (1H, m), 4.55 (2H, m), 3.24 (2H, m), 3.0 (5H, m + s), 2.59 (1H, m), 2.39 (1H, m), 2.2 - 1.7 (4H, m), 1.65 (1H, m), 1.40 (9H, s).

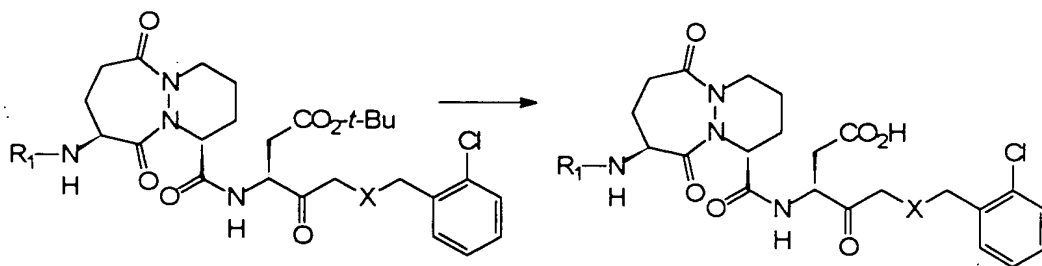
[3S(1S,9S)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-(5,7-dichlorobenzoxazol-2-yl)-4-oxobutanoate (222e), was prepared from 221e by an analogous method as that used for compound 216e to afford a colourless glass (480mg, 84%): $[\alpha]_D^{25}$ -86.4 ° (c 0.1 CH₂Cl₂); IR (KBr) 3337, 2978, 2938, 1728, 1657, 1534, 1456, 1422, 1395, 1370, 1277, 1250, 1154; ¹H NMR (CDCl₃) δ 7.80 (3H, m), 7.50 (4H, m), 7.20 (1H, d), 7.02 (1H, d), 5.60 (1H, m), 5.28 (1H, m), 5.15 (1H, m), 4.11 (1H, m), 3.34 (2H, m), 2.96 (3H, m), 2.40 (1H, m), 2.20 (1H, m), 1.92 (2H, m), 1.67 (2H, m), 1.38 (9H, s). MS ES⁻ Da/e 684 (M - 1)⁻ Cl³⁵ 47%, 686 (M - 1)⁻ Cl³⁷ 32%.

[3S(1S,9S)] 4-(5,7-Dichlorobenzoxazol-2-yl)-3-(6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (223b), was prepared from 222b by an analogous method as that used for compound 217e to afford an off-white solid (257mg, 78%): $[\alpha]_D^{25}$ -105.7 ° (c 0.1, CH₂Cl₂); IR (KBr) 3321,

- 404 -

1723, 1663, 1407, 1325, 1151, 992; ^1H NMR ($\text{D}_6\text{-DMSO}$) δ 8.96 (1H, d), 8.18 (1H, d), 7.96 (1H, d), 5.50 (1H, m), 5.15 (1H, m), 4.30 (2H, m), 3.06 (2H, m), 2.87 (5H, m + s), 2.29 (1H, m), 1.99 (4H, m), 1.56 (2H, m).

- 5 [3*S*(1*S*,9*S*)] 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-*a*][1,2]diazepine-1-carboxamido)-4-(5,7-dichlorobenzoxazol-2-yl)-4-oxobutanoic acid (223e), was prepared from 222e by an analogous method as that used
 10 for compound 217e to afford a pale cream solid (311mg, 78%): mp 167-180 °C; $[\alpha]_{\text{D}}^{23}$ -88.6 ° (c 0.1 CH_2Cl_2); IR (KBr) 3331, 1724, 1658, 1534, 1458, 1421, 1279, 1256, 991; ^1H NMR (CDCl_3) δ 7.77 (4H, m), 7.4 (5H, m), 5.57 (1H, bs), 5.33 (1H, bs), 5.47 (1H, q), 4.56 (1H, bd),
 15 3.60 (2H, m), 3.20 (3H, m), 2.76 (1H, m), 2.36 (1H, dd), 2.0 (3H, m), 1.66 (1H, m). MS ES Da/e 628 ($\text{M} - 1$) $^-$ Cl^{35} 7%, 630 ($\text{M} - 1$) $^-$ Cl^{37} 2.3%, 584 100%.



224e $\text{R}_1 = \text{PhCO}$, $\text{X} = \text{S}$

225e $\text{R}_1 = \text{PhCO}$, $\text{X} = \text{O}$

226e $\text{R}_1 = \text{PhCO}$, $\text{X} = \text{S}$

227e $\text{R}_1 = \text{PhCO}$, $\text{X} = \text{O}$

- 20 [3*S*(1*S*,9*S*)] *t*-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]-diazepine-1-carboxamido)-5-(2-chlorophenyl)methylthio-4-oxopentanoate (224e). 1-Hydroxybenzotriazole (0.23g,

- 405 -

1.71mmol) and ethyl dimethylaminopropyl carbodiimide hydrochloride was added to a stirred solution of the acid **212e** (0.295g, 0.853mmol) in THF (5ml). After 5min water (0.5ml) was added followed, after a further 7min, by the addition of a solution of (3S) t-butyl-3-allyloxycarbonylamino-5-(2-chloro-phenyl)methylthio-4-oxopentanoate (**123**, 0.478g, 1.02mmol) and (PPh₃)₂PdCl₂ (20mg) in THF (2ml). Tributyltin hydride (0.65ml, 2.33mmol) was added dropwise during 20min. The mixture was kept for 4.5h then diluted with EtOAc, washed with 1M HCl, brine, sat. aq. NaHCO₃ and then brine again. The mixture was dried (MgSO₄) and concentrated. The residue was triturated several times with hexane, which was decanted and discarded, then purified by flash chromatography (10-100% EtOAc in CH₂Cl₂) to afford 0.2g (35%) of a white glassy solid: mp 70-72 °C; [α]_D²⁶ - 82.5 ° (c 0.02, CH₂Cl₂). IR (KBr) 3404, 1726, 1660, 1534, 1524, 1422, 1277, 1254, 1154; ¹H NMR (CDCl₃) δ 7.83-7.78 (2H, m), 7.7, 7.75-7.32, 7.26-7.20 (7H, 3m), 7.12 (1H, d, J = 8.2), 7.01 (1H, d, J = 7.3), 5.23-5.08 (2H, m), 5.03-4.94 (1H, m), 4.62 (1H, dt, J = 14.5), 3.78 (2H, m), 3.38-3.29 (1H, m), 3.26 (2H, s), 3.06-2.82 (4H, m), 2.71 (1H, dd, J = 17.2, 4.5), 2.39 (1H, dd, J = 13.2, 6.5), 2.15-1.83, 1.73-1.63 (5H, m), 1.45 (9H, s). Anal. Calcd for C₃₃H₃₉ClN₄O₇S: C, 59.05; H, 5.86; N, 8.35. Found: C, 59.00; H, 5.80; N, 7.92.

[3RS, (1S,9S)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2-chlorophenylmethyloxy)-4-oxopentanoate (**225e**), was prepared from acid **212e** and (3S) t-butyl N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenylmethyloxy)-4-oxopentanoate (**201**) using a

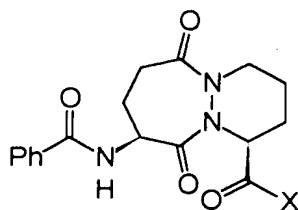
- 406 -

method similar to that used for compound **224e**, to afford 40mg (23%) of a glassy solid: ^1H NMR (CDCl_3) δ 7.83-7.73 (2H, m), 7.67-7.10 (9H, m), 5.23-5.09 (2H, m), 4.59 (1H, m), 4.45-4.22 (2H, m), 3.7-3.19, 3.08-
 5 2.72, 2.71-2.47, 2.05-1.85, 1.72-1.61, 1.45-1.26 (20H, 6m).

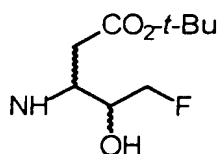
[**3S(1S,9S)**] 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2-chlorophenyl)methylthio-
 10 4-oxopentanoic acid (**226e**), was prepared from **224e** by an analogous method as that used for compound **217e** which afforded 0.22g (81%) of an off-white solid: mp 95-100 °C; $[\alpha]_{\text{D}}^{23}$ -95.6 ° (c 0.2, CH_2Cl_2). IR (KBr) 3393, 1720, 1658, 1529, 1422, 1279; ^1H NMR (D_6 -DMSO) δ
 15 8.80 (1H, d, J = 7.5), 7.89 (2H, m), 7.7 (1H, d, J = 7.7), 7.56-7.28 (7H, m), 5.10 (1H, m), 4.87-4.73 (2H, m), 4.39 (1H, m), 3.77 (2H, m), 3.44, 3.35 (2H, + H_2O , 2m), 2.97-2.56, 2.2, 1.92, 1.61 (11H, 4m). Anal. Calcd for $\text{C}_{29}\text{H}_{31}\text{ClN}_4\text{O}_7\text{S} \cdot 0.5\text{H}_2\text{O}$: C, 55.02; H, 5.10; N, 8.85.
 20 Found: C, 55.00; H, 5.09; N, 8.71.

[**3RS, (1S,9S)**] 3-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2-chlorophenylmethyloxy)-4-oxopentanoic acid (**227e**), was prepared from **225e** by an
 25 analogous method as that used for compound **217e**. The product was further purified by flash chromatography (0-5% MeOH/ CH_2Cl_2) to afford 19mg (81%) of a glassy solid: ^1H NMR (CDCl_3) δ 7.79 (2H, m), 7.66-7.18 (9H, m), 5.30-5.10 (2H, m), 4.85 (1H, m), 4.65 (2H, m), 4.53
 30 (1H, m), 4.28 (2H, m), 3.28, 3.01, 2.72, 2.33, 1.94, 1.60 (11H, 6m). MS (ES^- , m/z) 597 ($\text{M}^+ - 1$, 100%).

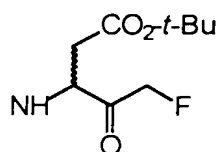
- 407 -



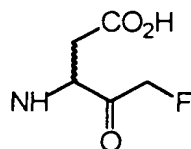
228e X =



229e X =



230e X =



[3*RS*,4*RS*(1*S*,9*S*)] *t*-Butyl 3-(9-benzoylamino-6,10-dioxo-
 5 1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino-
 [1,2-*a*][1,2]-diazepine-1-carboxamido)-5-fluoro-4-
 (228e). 1-Hydroxybenzotriazole (0.23g, 1.68mmol)
 followed by ethyldimethylaminopropyl carbodiimide
 hydrochloride (0.21g, 1.09mmol) were added to a stirred
 10 solution of the acid **212e** (0.29g, 0.84mmol) in CH₂Cl₂
 (3ml) at rt. The mixture was kept for 10min then a
 solution of (3*RS*,4*RS*) *t*-butyl 3-amino-5-fluoro-4-
 hydroxypentanoate (Revesz, L. et al. Tetrahedron Lett.,
 52, pp. 9693-9696 (1994); 0.29g, 1.40mmol) in CH₂Cl₂
 15 (3ml) was added followed by 4-dimethylaminopyridine

- 408 -

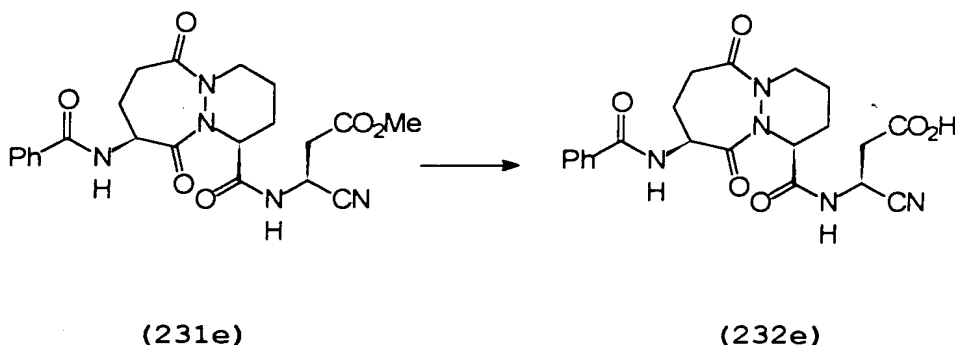
(10mg). The solution was stirred for 17h, diluted with EtOAc, washed with 1M HCl, brine, sat. aq. NaHCO₃ and brine again, dried (MgSO₄) and concentrated. The residue was purified by flash chromatography (50-100% EtOAc/CH₂Cl₂ and 5% MeOH/EtOAc) to afford 0.25g (56%) of a white glassy solid: IR (KBr) 3343, 1726, 1658, 1536, 1426, 1279, 1257, 1157; ¹H NMR (CDCl₃) δ 7.84-7.79 (2H, m), 7.57-7.40 (3H, m), 7.05-6.92, 6.73 (2H, 2m), 5.17-5.04 (2H, m), 4.56, 4.35-4.21, 4.04 (5H, 3m), 3.36, 3.09-2.34, 2.00 (11H, 3m), 1.46 (9H, s). Anal. Calcd for C₂₆H₃₅FN₄O₇ · 0.5H₂O: C, 57.45; H, 6.65; N, 10.31. Found: C, 57.64; H, 6.56; N, 10.15.

[3*RS*,4*RS*(1*S*,9*S*)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]-diazepine-1-carboxamido)-5-fluoro-4-oxypentanoate (229e) was prepared from 228c by an analogous method to that used for compound 216e. After purification by flash chromatography (30-50% EtOAc/CH₂Cl₂) the product was obtained as a white glassy solid (0.194g, 89%): IR (KBr) 3376, 1728, 1659, 1529, 1424, 1279, 1256, 1156.

[3*RS*, (1*S*,9*S*)] 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-fluoro-4-oxopentanoic acid (230e), was prepared from 229e by an analogous method to that used for compound 217e to afford 230e as a white glassy solid (100%): mp 105-125 °C; [α]_D²³ -91.4 ° (c 0.72, CH₃OH). IR (KBr) 3336, 1789, 1737, 1659, 1535, 1426, 1279, 1258, 1186; ¹H NMR (CD₃OD) δ 7.71-7.68 (2H, m), 7.37-7.23 (3H, m), 5.02, 4.88-4.63,

- 409 -

4.37-4.0 (6H, 3m), 3.30, 2.97, 2.68-2.60, 2.37-1.54 (11H, 4m). MS(ES⁻, m/z) 475 (M⁺ - 1, 100%).



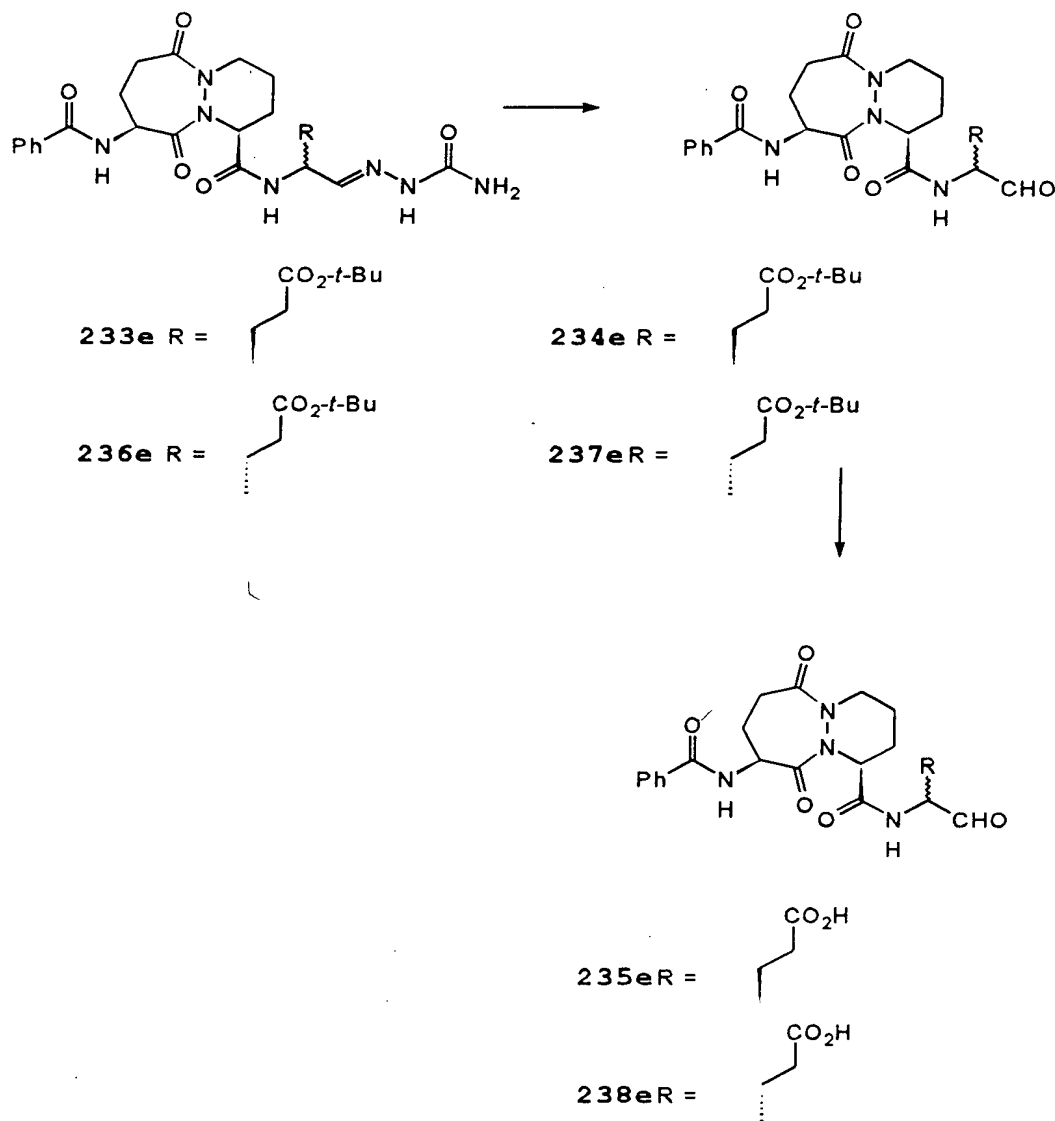
[3S(1S,9S)]-Methyl 9-(benzoylamino)-3-[6,10-dioxo-
 5 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-
 [1,2-a][1,2]diazepine-1-carboxamido]-3-cyanopropanoate
 (231e). N-Fluorenylmethyloxy-carbonyl-3-amino-3-
 cyanopropionic acid methyl ester (EP0547699A1, 385mg,
 1.1mmol) was treated with 17ml of diethylamine. After
 10 1.5h stirring at room temperature the solution was
 concentrated. The residue was chromatographed on
 silica gel (3% methanol in CH₂Cl₂) and gave the free
 amine as a pale yellow oil. To a solution of this oil
 and hydroxybenzotriazole (297mg, 2.19mmol) in DMF
 15 (5ml), was added at 0 °C ethyldimethylaminopropyl
 carbodiimide (232mg, 1.21mmol, 1.1 equiv) followed by
 (1S,9S) 9-(benzoylamino)-[6,10-dioxo-1,2,3,4,7,8,9,10-
 octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-
 carboxylic acid (212e). After stirring at 0 °C for 5
 20 min and then at room temperature overnight, the mixture
 was diluted with CH₂Cl₂ (50ml) and the resulting
 solution washed successively with 1M HCl (2 x 30ml),
 H₂O (30ml), 10% NaHCO₃ (2 x 30ml) and sat. aq. NaCl,
 dried (MgSO₄) and concentrated. Purification by flash

- 410 -

chromatography on silica gel (3% methanol in CH₂Cl₂) afforded the compound **231e** (404mg, 83%) as a solid: $[\alpha]_D^{20}$ -121 ° (c 0.14, CH₂Cl₂); ¹H NMR (CDCl₃) δ 7.40-7.83 (5H, m), 7.38 (1H, d), 6.96 (1H, d), 5.27-5.07 (2H, m), 4.66-4.50 (1H, m), 3.79 (3H, s), 3.23-2.73 (6H, m), 2.47-2.33 (1H, m), 2.15-1.82 (4H, m); Anal. Calcd for C₂₂H₂₅N₅O₆: C, 58.0; H, 5.53; N, 15.38. Found: C, 57.6; H, 5.6; N, 15.0.

[3S(1S,9S)] 9-(Benzoylamino)-3-[6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido]-3-cyanopropanoic acid (232e). A solution of methyl ester **231e** (400mg, 0.88mmol) in methanol (30ml) and water (30ml) was cooled at 0 °C and treated with diisopropylethylamine. The solution was stirred at 0 °C for 10min and then at room temperature overnight. The heterogeneous mixture was concentrated and the solid obtained was chromatographed on silica gel (5% methanol/1% formic acid in CH₂Cl₂) affording the free acid **232e** (170mg, 44%) as a white solid: mp 155 °C (dec); $[\alpha]_D^{20}$ -117 ° (c 0.1, MeOH); IR (KBr) 3343, 3061, 2955, 1733, 1656, 1577, 1533, 1490, 1421, 1342, 1279, 1256, 1222, 1185, 708; ¹H NMR (D⁴-MeOH) δ 7.88-7.28 (5H, m), 5.20-5.03 (1H, m), 4.98-4.84 (2H, m), 4.75-4.53 (1H, m), 4.51-4.34 (1H, m), 3.45-3.22 (1H, m), 3.14-2.94 (1H, m), 3.14-2.94 (1H, m), 2.88-2.61 (2H, m), 2.53-1.50 (8H, m); Anal. Calcd for C₂₁H₂₃N₅O₆ · 1.5H₂O: C, 53.84; H, 5.59; N, 14.95; O, 25.61. Found: C, 54.3; H, 5.4; N, 14.3.

- 411 -



[4*S*, (1*S*,9*S*)] *t*-Butyl 4-[9-(benzoylamino)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido]-5-oxopentanoate semicarbazone (**233e**). A solution of (1*S*,9*S*) 6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-9-(benzoylamino)-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxylic acid (**212e**) (345mg, 1.0mmol), (4*S*) *t*-butyl *N*-

- 412 -

(allyloxycarbonyl)-4-amino-5-oxopentanoate semicarbazone (**208a**) (361mg, 1.1mmol, 1.1 equiv) and $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ (20mg) in CH_2Cl_2 (5ml), was treated dropwise with $n\text{-Bu}_3\text{SnH}$ (0.621ml, 2.3mmol, 2.1 equiv).
 5 The resulting orange brown solution was stirred at 25 °C for 10min and then 1-hydroxybenzotriazole (297mg, 2.2mmol, 2 equiv) was added. The mixture was cooled to 0 °C and ethyldimethylaminopropyl carbodiimide (253mg, 1.3mmol, 1.2 equiv) added. After stirring at 0 °C for
 10 10min and then at room temperature overnight, the mixture was diluted with EtOAc (50ml) and the resulting solution washed successively with 1M HCl (3 x 25ml), 10% NaHCO_3 (3 x 25ml) and sat. aq. NaCl, dried (MgSO_4) and concentrated. Flash chromatography on silica gel
 15 (2-10% methanol in CH_2Cl_2) afforded compound **233e** (280mg, 49%) as a tan solid: $[\alpha]_{\text{D}}^{20} -95$ (c 0.09, MeOH); IR (KBr) 3477, 3333, 2968, 2932, 1633, 1580, 1535, 1423, 1378, 1335, 1259, 1156, 1085, 709; ^1H NMR (CDCl_3) δ 9.32 (1H, s), 7.83-7.39 (6H, m), 7.11-7.09 (1H, m),
 20 6.30-5.30 (2H, brs), 5.17-5.05 (2H, m), 4.62-4.38 (2H, m), 3.30-3.15 (1H, m), 3.13-2.65 (2H, m), 2.46-2.19 (3H, m), 2.15-1.54 (8H, m), 1.42 (9H, s).

[4*R*, (1*S*,9*S*)] *t*-Butyl 4-[9-(benzoylamino)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino-
 25 [1,2-*a*][1,2]diazepine-1-carboxamido]-5-oxopentanoate semicarbazone (**236e**), was prepared by an analogous method to that used for **233e** using (4*R*) *t*-butyl *N*-allyloxycarbonyl-4-amino-5-oxo-pentanoate semicarbazone (**208b**, 435mg, 1.33mmol). The product was obtained as a
 30 foam (542mg, 71%): $[\alpha]_{\text{D}}^{20} -99$ ° (c 0.19, CHCl_3); IR (KBr) 3473, 3331, 3065, 2932, 2872, 1660, 1580, 1533, 1488, 1423, 1370, 1337, 1278, 1254, 1223, 1155, 1080,

- 413 -

1024, 983, 925, 877, 846, 801, 770, 705; ^1H NMR (CDCl_3)
 δ 9.42 (1H, s), 7.81 (2H, d), 7.51-7.40 (4H, m), 7.06
 (1H, d), 6.50-5.50 (2H, broad s), 5.25-5.00 (2H, m),
 4.60-4.45 (2H, m), 3.15-2.85 (2H, m), 2.75-2.35 (1H,
 5 m), 2.30-1.23 (11H, m), 1.42 (9H, s).

[4*S*, (1*S*,9*S*)] *t*-Butyl 4-[9-(benzoylamino)-6,10-dioxo-
 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-
 [1,2-*a*][1,2]diazepine-1-carboxamido]-5-oxopentanoate
 (234*e*). A solution of semicarbazone 233*e* (390mg,
 10 0.68mmol) in methanol (10ml) was cooled at 0 °C and
 then treated with a 38% aq. solution of formaldehyde
 (2ml) and 1M HCl (2ml). The reaction mixture was then
 stirred overnight at room temperature. The solution
 was concentrated to remove the methanol. The aq.
 15 solution was extracted with EtOAc (30ml). The organic
 solution was successively washed with 10% NaHCO_3 (30ml)
 and sat. aq. NaCl (30ml), dried (MgSO_4) and
 concentrated. Purification by flash chromatography on
 silica gel (2-5% methanol in CH_2Cl_2) afforded 234*e*
 20 (179mg, 51%) as a white foam: $[\alpha]_{\text{D}}^{20}$ -101 ° (c 0.064,
 MeOH); IR (KBr) 3346, 2976, 2934, 1730, 1657, 1535,
 1456, 1425, 1278, 1255, 1156, 708; ^1H NMR (CDCl_3) δ
 9.56 (1H, s), 7.88-7.38 (5H, m), 7.01 and 6.92 (2H,
 2d), 5.27-5.08 (2H, m), 4.69-4.46 (1H, m), 3.50-3.27
 25 (2H, m), 3.15-2.73 (2H, m), 2.46-1.83 (10H, m), 1.45
 (9H, s).

[4*R*, (1*S*,9*S*)] *t*-Butyl 4-[9-(benzoylamino)-6,10-dioxo-
 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-
 [1,2-*a*][1,2]diazepine-1-carboxamido]-5-oxopentanoate
 30 (237*e*), was prepared from 236*e* by an analogous method
 to 234*e* to afford a white foam (390mg, 85%): $[\alpha]_{\text{D}}^{20}$

- 414 -

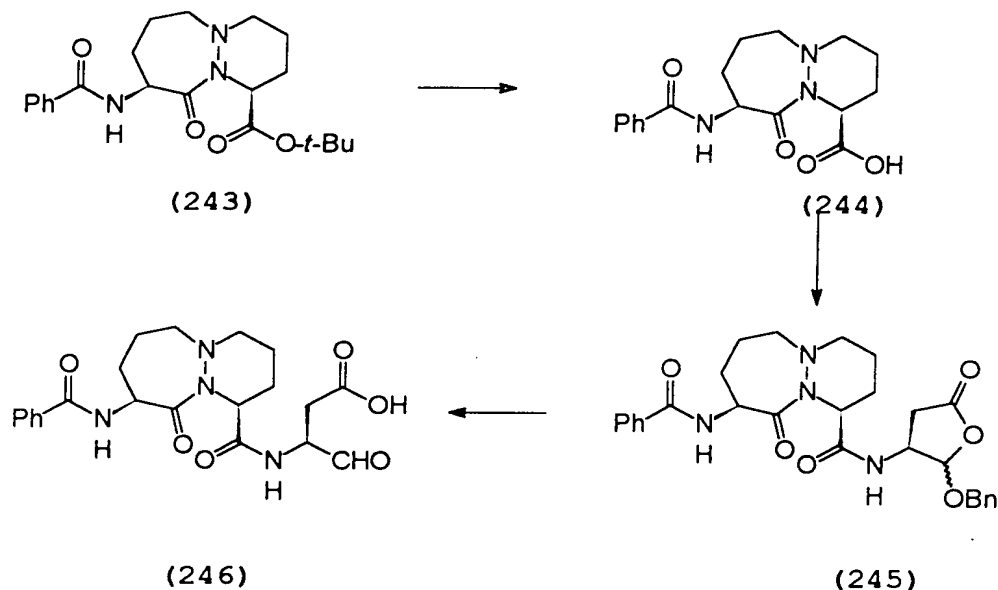
-113 ° (c 0.242, CHCl₃); IR (KBr) 3352, 3065, 2974, 1729, 1657, 1536, 1489, 1454, 1423, 1369, 1338, 1278, 1255, 1223, 1156, 1078, 1026, 981, 846, 709.

[4*S*, (1*S*,9*S*)] 4-[9-(Benzoylamino)-6,10-dioxo-
5 1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino-
[1,2-*a*][1,2]diazepine-1-carboxamido]-5-oxopentanoic
acid (**235e**). A solution of *t*-butyl ester **234e** (179mg,
0.35mmol) in dry CH₂Cl₂ (3ml) was cooled to 0 °C and
treated with trifluoroacetic acid (2ml). The resulting
10 solution was stirred at 0 °C for 30min and then at room
temperature for 2h. The solution was concentrated, the
residue taken up in dry CH₂Cl₂ (5ml) and the mixture
again concentrated. This process was repeated once
again with more CH₂Cl₂ (5ml). The residue obtained was
15 crystallized in diethyl ether. The precipitate was
collected and purified on silica gel column (5%
methanol in CH₂Cl₂) which afforded compound **235e** as a
white solid (111mg, 70%): mp 142 °C (dec); [α]_D²⁰ -85.5
(c 0.062, MeOH); IR (KBr) 3409, 3075, 2952, 1651, 1541,
20 1424, 1280, 1198, 1136, 717; ¹H NMR (D₆-DMSO) δ 9.40
(1*H*, s), 8.62 (2*H*, m), 7.96-7.38 (5*H*, m), 5.19-5.02
(1*H*, m), 4.98-4.79 (1*H*, m), 4.48-4.19 (1*H*, m), 3.51-
3.11 (2*H*, m), 3.04-2.90 (2*H*, m), 2.38-1.46 (10*H*, m).

[4*R*, (1*S*,9*S*)] 4-[9-(Benzoylamino)-6,10-dioxo-
25 1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino-
[1,2-*a*][1,2]diazepine-1-carboxamido]-5-oxopentanoic
acid (**238e**), was prepared from **237e** by an analogous
route to **235e** which afforded a beige foam (190mg, 60%):
[α]_D²⁰ -78 (c 0.145, MeOH); IR (KBr) 3400, 3070, 2955,
30 2925, 2855, 1653, 1576, 1541, 1490, 1445, 1427, 1342,
1280, 1258, 1205, 1189, 1137, 1075, 1023, 983, 930,

- 415 -

878, 843, 801, 777, 722; ^1H NMR ($\text{D}_6\text{-DMSO}$) δ 9.40 (1H, s), 8.72-8.60 (2H, m), 7.89 (2H, d), 7.56-7.44 (3H, m), 5.17 (1H, m), 4.90-4.83 (1H, m), 4.46-4.36 (1H, m), 4.20-4.15 (1H, m), 3.40-3.30 (1H, m), 2.98-2.90 (2H, m), 2.50-1.60 (10H, m).



(1*S*,9*S*) *t*-Butyl 9-benzoylamino-octahydro-10-oxo-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxylate (243),
 10 was prepared from (1*S*,9*S*) *t*-butyl 9-amino-octahydro-10-oxo-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxylate (Attwood, et al. J. Chem. Soc., Perkin 1, pp. 1011-19 (1986)), by the method described for 211e, to afford 2.03g (86%) of a colourless foam: $[\alpha]_{\text{D}}^{25} -15.9^\circ$ (c 0.5, CH_2Cl_2); IR (KBr) 3400, 2976, 2937, 1740, 1644, 1537, 1448, 1425, 1367, 1154; ^1H NMR (CDCl_3) δ 7.88-7.82 (2H, m), 7.60-7.38 (4H, m), 5.48 (1H, m), 4.98 (1H, m), 3.45 (1H, m), 3.22-2.96 (2H, m), 2.64 (1H, m), 2.43-2.27 (2H, m), 1.95 (2H, m), 1.82-1.36 (4H, m),
 20 1.50 (9H, s); Anal. Calcd for $\text{C}_{21}\text{H}_{29}\text{N}_3\text{O}_4 \cdot 0.25\text{H}_2\text{O}$: C,

- 416 -

64.35; H, 7.59; N, 10.72. Found: C, 64.57; H, 7.43; N, 10.62. MS (ES +, m/z) 388 (100%, $M^+ + 1$).

(1*S*,9*S*) 9-Benzoylamino-octahydro-10-oxo-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxylic acid

5 **(244)**, was prepared from (1*S*,9*S*) *t*-butyl 9-benzoylamino-octahydro-10-oxo-6H-pyridazino-[1,2-*a*][1,2]diazepine-1-carboxylate (**243**), by the method described for **212e**, to afford 1.52g (89%) of a white powder: mp. 166-169 °C (dec); $[\alpha]_D^{25}$ -56.4 ° (c
10 0.5, CH₃OH); IR (KBr) 3361, 2963, 2851, 1737, 1663, 1620, 1534, 1195, 1179; ¹H NMR (D₆-DMSO) δ 12.93 (1H, brs), 8.44 (1H, d, *J* = 8.4), 7.93 (2H, m), 7.54 (3H, m), 5.46 (1H, m), 4.87 (1H, m), 3.12 (2H, m), 2.64 (1H, m), 2.64 (1H, m), 2.27 (1H, m), 1.98-1.68 (7H, m), 1.40
15 (1H, m); Anal. Calcd for C₁₇H₂₁N₃O₄ · 0.25H₂O: C, 60.79; H, 6.45; N, 12.51. Found: C, 61.07; H, 6.35; N, 12.55. MS (ES+, m/z) 332 (58%, $M^+ + 1$), 211 (100).

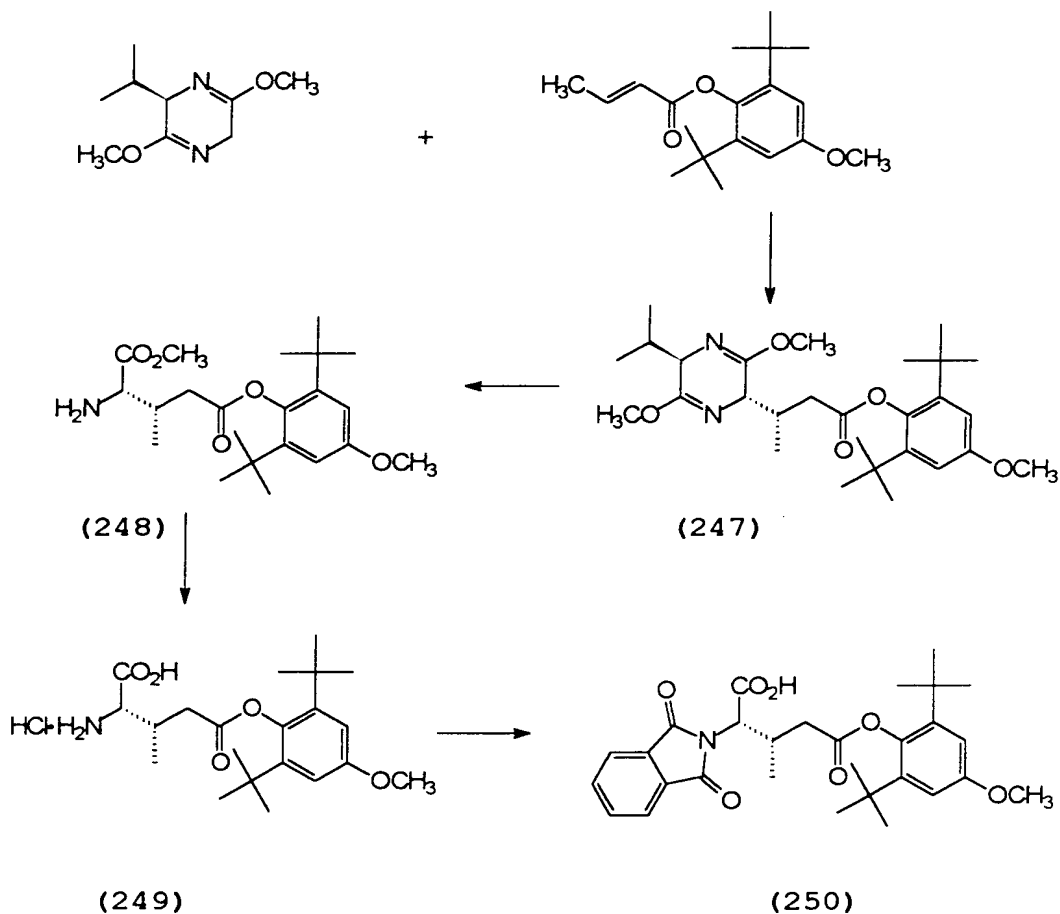
[3*S*,2*RS*(1*S*,9*S*)] N-(2-Benzylloxy-5-oxotetrahydrofuran-3-yl)-9-benzoylamino-octahydro-10-oxo-6H-

20 **pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide (245)**, was prepared from (1*S*,9*S*) 9-benzoylamino-octahydro-10-oxo-6H-pyridazino[1,2-*a*][1,2]-diazepine-1-carboxylic acid (**244**), by the method described for **213e**, to afford 601mg (76%) of a colourless foam: IR (KBr) 3401, 2945,
25 1794, 1685, 1638, 1521, 1451, 1120; ¹H NMR (CDCl₃) δ 7.87-7.77 (2H, m), 7.57-7.14 (10H, m), 5.59-5.47 (2H, m), 4.97-4.32 (4H, m), 3.27-1.35 (14H, m); Anal. Calcd for C₂₈H₃₂N₄O₆ · 0.5H₂O: C, 63.50; H, 6.28; N, 10.58. Found: C, 63.48; H, 6.14; N, 10.52. MS (ES +, m/z)
30 521 (100%, $M^+ + 1$).

- 417 -

[3*S*(1*S*,9*S*)] 3-(9-Benzoylamino-octahydro-10-oxo-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide-4-oxobutanoic acid (246), was prepared from [3*S*, 2*RS*(1*S*,9*S*)]N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-9-benzoylamino-octahydro-10-oxo-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide (245), by the method described for 214e, to afford 396mg (84%) of a white powder: mp. 110-115 °C; $[\alpha]_D^{26}$ -126.3 ° (c 0.2, CH₃OH); IR (KBr) 3345, 2943, 1787, 1730, 1635, 1578, 1528, 1488, 1450, 1429; ¹H NMR (CD₃OD) δ 7.88 (2H, m), 7.48 (3H, m), 5.55 (1H, m), 4.91 (1H, m), 4.56 (1H, m), 4.29 (1H, m), 3.41-3.05 (3H, m), 2.76-2.41 (3H, m), 2.28-2.01 (3H, m), 1.86-1.65 (4H, m), 1.36 (1H, m); Anal. Calcd for C₂₁H₂₆N₄O₆ · 1.25H₂O: C, 55.68; H, 6.34; N, 12.37. Found: C, 55.68; H, 6.14; N, 12.16. MS (ES⁻, m/z) 429 (100%, M⁺ - 1).

- 418 -



[(3*S*(2*R*, 5*S*))-2,6-Di-*tert*-butyl-4-methoxyphenyl-3-[5-(2,5-dihydro-3,6-dimethoxy-2-(1-methylethyl)pyrazinyl)]butanoate (247). *n*-Butyllithium (1.6M in hexane) (22.3ml, 35.7mmol) was added dropwise over 20min to a solution of (2*R*)-(-)-2,5-dihydro-3,6-dimethoxy-2-(1-methylethyl)pyrazine (5.8ml, 6.0g, 32.4mmol) in THF (250ml) cooled to -75 °C at a rate such that the temperature was maintained below -72 °C. The reaction mixture was stirred for 1h at -75 °C and a solution of 2,6-di-*t*-butyl-4-methoxyphenyl-2-butenate (Suzuck et al. Liebigs Ann. Chem. pp. 51-61 (1992))

- 419 -

(9.9g, 32.5mmol) in THF (60ml) was added over 30 minutes maintaining the temperature below -72 °C during the addition. The reaction mixture was kept at -75 °C for 1.5h and a solution of glacial acetic acid (6ml) in THF (25ml) was added at -75 °C and the solution warmed to room temperature. The solution was poured onto 10% NH₄Cl (300ml) and extracted with diethyl ether (3 x 250ml). The combined organic phases were washed with brine (2 x 200ml), dried over Na₂SO₄ and evaporated to dryness under reduced pressure. The residual oil was purified by flash chromatography on silica gel (20% heptane in CH₂Cl₂) which afforded the title compound as a light yellow oil (13.5g, 85%): $[\alpha]_D^{20}$ -64 ° (c 0.22, MeOH); IR (KBr) 2962, 2873, 2840, 1757, 1697, 1593, 1460, 1433, 1366, 1306, 1269, 1236, 1187, 1157, 1126, 1063, 1038, 1011, 970, 924, 892, 867, 846, 831, 797, 773, 754; ¹H NMR (CDCl₃) δ 6.85 (2H, s), 4.21 (1H, t, *J* = 3.5), 3.98 (1H, t, *J* = 3.5), 3.79 (3H, s), 3.71 (3H, s), 3.69 (3H, s), 3.15 (1H, dd, *J* 17.8, 7.9), 2.86-2.81 (1H, m), 2.58 (1H, dd, *J* = 17.8, 5.9), 2.28-2.19 (1H, m), 1.33 (18H, s), 1.02 (3H, d, *J* = 6.8), 0.70 (6H, dd, *J* = 13, 6.8).

(2*S*,3*S*)-5-[2,6-Di-*t*-butyl-4-methoxyphenyl]1-methyl-3-methylglutamate (248). A solution of [3*S*(2*R*, 5*S*)]-2,6-di-*t*-butyl-4-methoxyphenyl-3-[5-(2,5-dihydro-3,6-dimethoxy-2-(1-methylethyl)pyrazinyl)]butanoate (**247**) (22.4g, 45.8mmol) in acetonitrile (300ml) and 0.25N HCl (366ml, 2 equiv) was stirred at room temperature under nitrogen atmosphere for 4 days. The acetonitrile was evaporated under reduced pressure and diethylether (250ml) was added to the aq. phase. The pH of the aq. phase was adjusted to pH8-9 with concentrated ammonia

- 420 -

solution (32%) and the phases separated. The aq. phase was extracted with diethylether (2 x 250ml). The combined organic phases were dried over Na₂SO₄ and evaporated to dryness under reduced pressure. The residual oil was purified by flash chromatography on silica gel (2% methanol in CH₂Cl₂) which afforded the required product as a light yellow oil (8.2g, 45%):

5 $[\alpha]_D^{20} +20^\circ$ (c 0.26, MeOH); IR(KBr) 3394, 3332, 3000, 2962, 2915, 2877, 2838, 1738, 1697, 1593, 1453, 1430, 1419, 1398, 1367, 1304, 1273, 1251, 1221, 1203, 1183, 1126, 1063, 1025, 996, 932, 891, 866, 847, 800, 772, 745; ¹H NMR (CDCl₃) δ 6.85 (2H, s), 3.79 (3H, s), 3.74 (3H, s), 3.72-3.69 (1H, m), 3.05-2.85 (1H, m), 2.67-2.50 (2H, m), 1.32 (18H, s), 0.93 (3H, d, $J = 7$); Anal.

15 Calcd for C₂₂H₃₅NO₅: C, 67.15; H, 8.96; N, 3.56. Found: C, 67.20; H, 9.20; N, 3.70.

(2*S*,3*S*)-5-[2,6-Di-*t*-butyl-4-methoxyphenyl]3-methylglutamate (249). A solution of (2*S*,3*S*)-5-[2,6-di-*t*-butyl-4-methoxyphenyl]3-methylglutamate (248)

20 (8.0g, 20.3mmol) in 5N HCl (200ml) was heated at reflux for 2h. The reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in cyclohexane (x4) and evaporated to dryness (x4) which afforded a white solid (7.9g, 93%): mp 230 °C; $[\alpha]_D^{20} +22^\circ$ (c 0.27, MeOH); IR (KBr) 3423, 2964, 1755, 1593, 1514, 1456, 1421, 1371, 1303, 1259, 1201, 1179, 1138, 1106, 1060, 966, 926, 861, 790, 710; ¹H NMR (MeOD) δ 6.76 (2H, s), 4.02 (1H, d, $J = 3.7$), 3.67 (3H, s), 3.05-2.85 (1H, m), 2.80-2.55 (2H, m), 1.22 (18H, s), 1.09 (3H, d, $J = 6.3$); ¹³C NMR (MeOD) δ 174.5, 171.4,

30 158.6, 145.2, 143.1, 113.2, 58.3, 56.3, 39.8, 36.9,

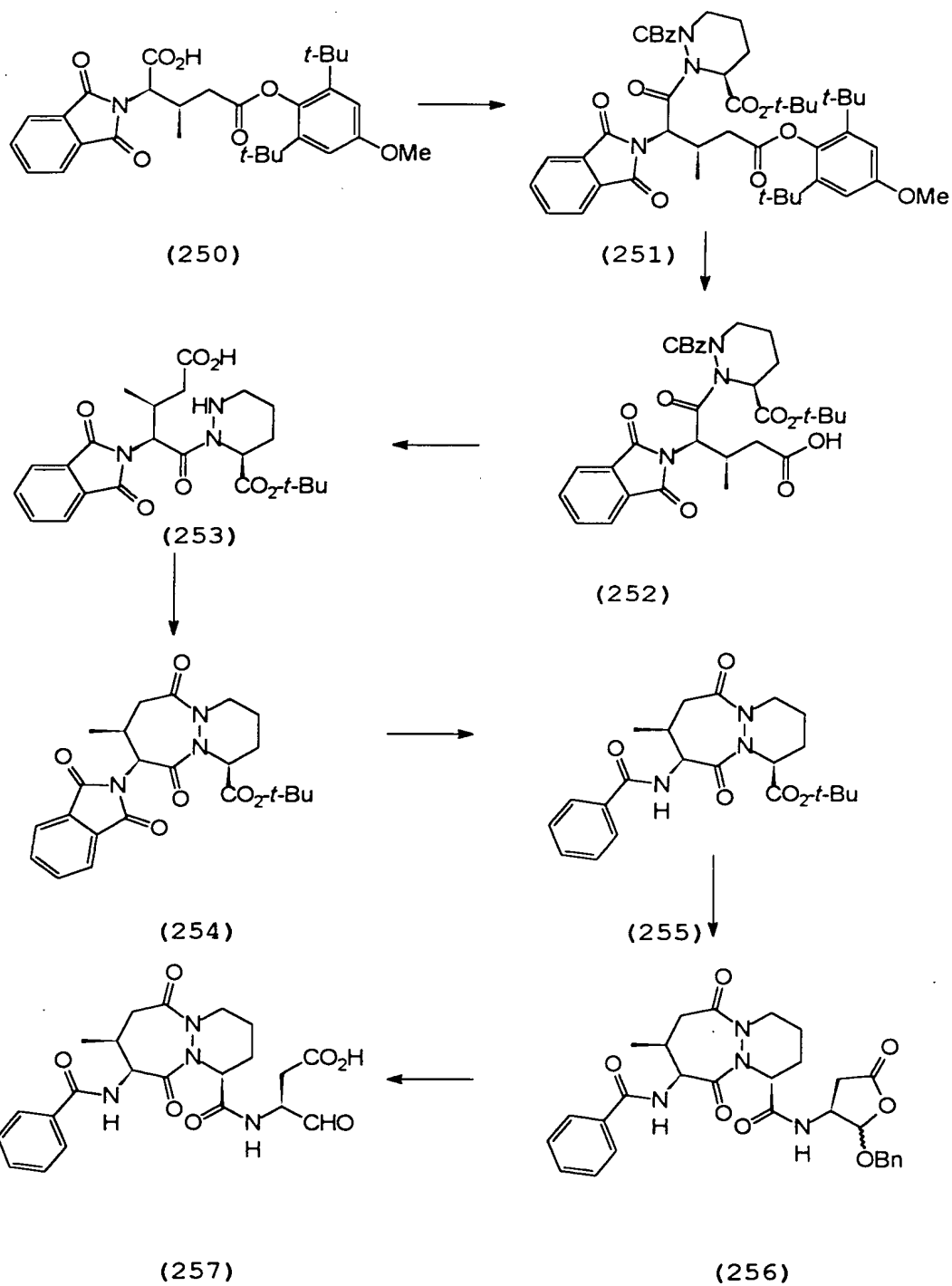
- 421 -

32.5, 16.6; Anal. Calcd for $C_{21}H_{34}ClNO_5$: C, 60.64; H, 8.24; N, 3.37. Found: C, 60.80; H, 8.40; N, 3.40.

(2*S*,3*S*)-5-[2,6-Di-*t*-butyl-4-methoxyphenyl]3-methyl-2-phthalimido-1,5-pentanedioate (250),

5 Diisopropylethylamine (4.1ml, 3.04g, 23.5mmol, 1.25 equiv) and phthalic anhydride (3.5g, 23.6mmol, 1.25 equiv) were added to a solution of (2*S*,3*S*)-5-[2,6-di-*t*-butyl-4-methoxyphenyl]3-methylglutamate (**249**) (7.8g, 18.6mmol) in toluene (300ml). and the resulting mixture
10 was heated at reflux for 3 hours. After cooling to room temperature, the reaction mixture was evaporated to dryness and the resulting oil purified by flash chromatography on silica gel (2% methanol in CH_2Cl_2) which afforded the required product as a white foam
15 (8.35g, 87%): $[\alpha]_D^{20}$ -20 ° (c 1.04, MeOH); IR (KBr) 3480, 2968, 2880, 1753, 1721, 1594, 1462, 1422, 1388, 1303, 1263, 1216, 1183, 1148, 1062, 1003, 933, 899, 755, 723; 1H NMR ($CDCl_3$) δ 7.92-7.87 (2H, m), 7.78-7.73 (2H, m), 6.84 (2H, s), 4.95 (1H, d), 3.78 (3H, s),
20 3.30-3.05 (2H, m), 2.85-2.65 (1H, m), 1.30 (18H, s), 1.13 (3H, d).

- 422 -



- 423 -

1-(2,6-di-*t*-Butyl-4-methoxy)-phenyl-5-(1-benzyloxycarbonyl-3-*t*-butoxycarbonyl-hexahydro-pyridazin-2-yl)-3-methyl-4-phthalimidopentan-1,5-dioate (251). A solution of the amino acid (250) (1.2g, 2.35mmol) in dry diethylether (10ml) was treated with phosphorus pentachloride (0.52g, 2.5mmol) at room temperature for 2h. The mixture was concentrated and treated several times with toluene and again evaporated to dryness. The resulting acid chloride was dissolved in dry THF (5ml) and CH₂Cl₂ (5ml) and cooled to 0 °C. *t*-Butyl-1-(benzyloxycarbonyl)-hexahydro-3-pyridazine-carboxylate (0.753g, 2.35mmol, 1 equiv) and *N*-ethylmorpholine (3ml) were added to the solution. The reaction mixture was stirred for 30min at 0 °C and then overnight at room temperature. The mixture was evaporated and the resulting residue taken up with CH₂Cl₂ (30ml). The solution was washed with 1M HCl, water, 10% NaHCO₃, dried (MgSO₄) and evaporated. The resulting white foam was purified on silica gel (0-2% methanol in CH₂Cl₂) which afforded the required compound 251 as a pale yellow glassy solid (740mg, 39%): $[\alpha]_D^{20}$ -22 (c 0.42, MeOH); IR (KBr) 3441, 2966, 1725, 1693, 1386, 1255, 1221, 1186, 1154, 1123, 1063, 724; ¹H NMR (CDCl₃) δ 7.94-7.89 (4H, m), 7.56-7.28 (5H, m), 6.84 (2H, 2s), 5.29-5.20 (2H, AB), 4.91-4.81 (1H, m), 4.05-3.88 (1H, m), 3.78 (3H, s), 3.75-3.80 (1H, m), 3.28-2.95 (2H, m), 2.23-1.51 (6H, m), 1.45 (9H, s), 1.31 (9H, s), 1.28 (9H, s), 1.27 (3H, d).

(1*S*, 8*S*, 9*S*) *t*-Butyl 6,10-dioxo-8-methyl-1,2,3,4,7,8,9,10-octahydro-9-phthalimido-6H-pyridazino[1,2-*a*][1,2]diazepin-1-carboxylate (254). A solution of the protected acid (251) (715mg, 0.893mmol)

- 424 -

in acetonitrile was treated with Cerium (IV) ammonium nitrate (1.8g, 3.3mmol, 3.7 equiv) in water (3ml) for 4h at room temperature. Mannitol (600mg, 3.3mmol, 3.7 equiv) was added and the mixture was stirred for 1h.

5 Diethylether (50ml) and water (30ml) were added to the mixture. After decantation, the aq. phase was extracted with diethylether (4 x 50ml). The combined organic phase was washed with water, dried (MgSO₄) and concentrated. Chromatography on silica gel (10%

10 methanol in CH₂Cl₂) afforded 5-(1-benzyloxycarbonyl-3-t-butoxycarbonyl-hexahydropyridazin-2-yl)carbonyl-3-methyl-4-phthalimidopentanoic acid (**252**) (360mg, 64%): $[\alpha]_D^{20}$ -49.2 (c 0.118, MeOH). This product was used without further purification (360mg, 0.609mmol), and

15 was hydrogenated in methanol (30ml) using 10% Pd/carbon (36mg) for 3h. The reaction mixture was filtered and the resulting solution concentrated to afford the amine (**253**) as a foam (270mg, 96%) $[\alpha]_D^{20}$ -56.1 (c 0.18 MeOH). The amine (**253**) was dissolved in dry THF (10ml) and

20 phosphorous pentachloride (305mg, 1.47mmol, 2.5 equiv) was added. The mixture was then cooled to -5 °C and N-ethylmorpholine was added under nitrogen. The reaction mixture was stirred overnight at room temperature. The mixture was concentrated and the residue taken up with

25 CH₂Cl₂ (20ml), cold H₂O (20ml), 1M HCl (20ml). After decantation, the aq. phase was reextracted with CH₂Cl₂ (2 x 20ml). The combined organic phase was washed with 10% NaHCO₃ and water, dried (MgSO₄) and concentrated. The resulting oil was purified on silica gel (1%

30 methanol in CH₂Cl₂) affording the bicyclic compound (**254**) as a solid (65mg, 25%): $[\alpha]_D^{20}$ -77 (c 0.208, MeOH); IR (KBr) 3471, 3434, 2975, 2928, 1767, 1723, 1443, 1389, 1284, 1243, 1151, 1112, 720; ¹H NMR (CDCl₃)

- 425 -

δ 7.94-7.69 (4H, m), 5.34-5.27 (1H, m), 4.89-4.66 (2H, m), 3.94-3.64 (2H, m), 3.02-2.84 (1H, m), 2.34-2.19 (2H, m), 1.94-1.61 (3H, m), 1.47 (9H, s), 1.14 (3H, d); Anal. Calcd for $C_{23}H_{27}N_3O_6$: C, 62.57; H, 6.17; N, 9.52.
5 Found: C, 62.60; H, 6.40; N, 9.10.

(1S, 8S, 9S) t-Butyl-9-benzoylamino-6,10-dioxo-8-methyl-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxylate (255). A solution
of the bicyclic compound (254) (70mg, 0.16mmol) in
10 ethanol was treated with hydrazine hydrate (0.02ml, 4mmol, 2.5 equiv). After 5h stirring at room temperature, the mixture was concentrated and the resulting residue taken up in toluene and reevaporated. The residue was treated with 2M acetic acid (2ml) for
15 16h. The resulting precipitate was filtered and washed with 2M acetic acid (10ml). The filtrate was basified with solid $NaHCO_3$ and then extracted with EtOAc. The organic solution was washed with water, dried ($MgSO_4$) and concentrated. Purification by flash chromatography
20 on silica gel (2% methanol in CH_2Cl_2) afforded the free amine as a foam (50mg, 100%). The amine (50mg, 0.16mmol) was dissolved in dioxane (1ml) and water (0.25ml) and treated with $NaHCO_3$ (0.034g, 0.04mmol) followed by benzoylchloride (0.047ml, 0.40mmol, 2.8
25 equiv). The mixture was stirred overnight at room temperature, then diluted with EtOAc (15ml). The organic solution was washed with 10% $NaHCO_3$ and sat. aq. $NaCl$, dried ($MgSO_4$) and concentrated. Purification by flash chromatography on silica gel (2% methanol in
30 CH_2Cl_2) afforded the benzamide 255 as a foam (67mg, 100%): 1H NMR ($CDCl_3$) δ 7.89-7.39 (5H, m), 6.79 (1H, d), 5.32-5.20 (1H, m), 4.98-4.82 (1H, m), 4.75-4.64

- 426 -

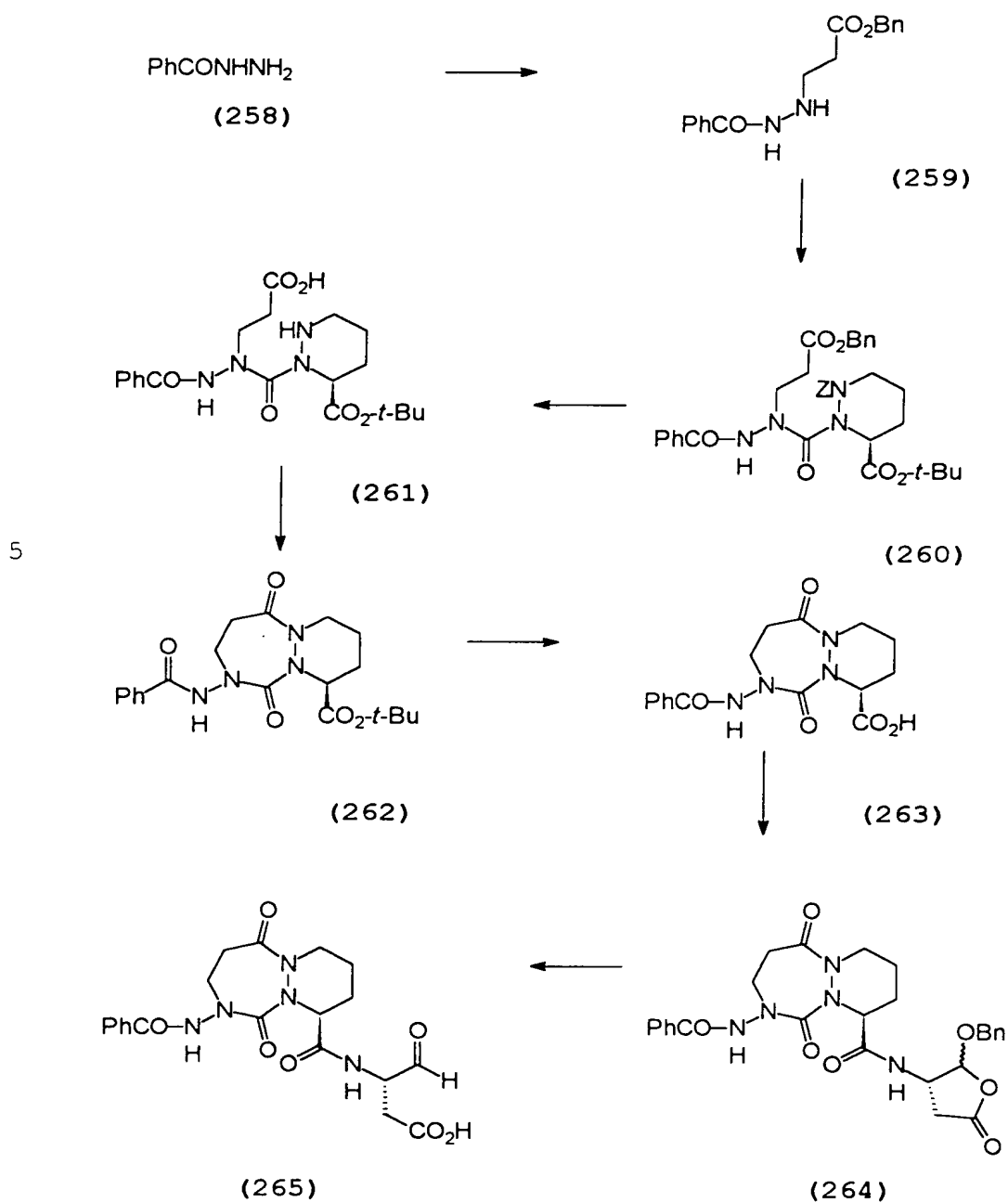
(1H, m), 3.84-3.65 (1H, m), 3.09-2.89 (1H, m), 2.45-2.18 (2H, m), 2.00-1.61 (4H, m), 1.48 (9H, s), 1.28 (3H, d).

[3S(1S, 8S, 9S)] 3-(9-benzoylamino-6,10-dioxo-8-methyl-
5 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-
[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid
(257). A solution of t-butyl ester 255 (67mg, 0.16mmol) in CH₂Cl₂ (1ml) was treated at 0 °C with trifluoroacetic acid (1ml). The resulting solution was
10 stirred at 0 °C for 15min and then at room temperature for 1h. The solution was concentrated, the residue taken up in dry CH₂Cl₂ (2 x 2ml) and the mixture again concentrated (x2). The residue was crystallized from diethylether. Filtration of the precipitate afforded
15 the free acid of 255 as a grey solid (40mg, 70%). A solution of acid (40mg, 0.11mmol), N-allyloxycarbonyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran (Chapman, Bioorg. & Med. Chem. Lett., 2, pp. 615-18 (1992); 39mg, 0.13mmol, 1.2equiv) and (Ph₃P)₂PdCl₂ (3mg) in a mixture
20 of dry CH₂Cl₂ (1ml) and dry DMF (0.2ml) was treated dropwise with n-Bu₃SnH (0.089ml, 0.33mmol, 3 equiv). The resulting solution was stirred at 25 °C for 10min and then 1-hydroxybenzotriazole (36mg, 0.266mmol, 2.4 equiv) was added. The mixture was cooled to 0 °C and
25 ethyldimethylaminopropyl carbodiimide (31mg, 0.16mmol, 1.5equiv) was added. After stirring at 0 °C for 10min and then at room temperature overnight, the mixture was diluted with EtOAc (20ml) and the resulting solution washed successively with 1M HCl (2 x 5ml), 10% NaHCO₃
30 (2 x 5ml) and sat. aq. NaCl (5ml), dried (MgSO₄) and concentrated. Flash chromatography on silica gel (2% methanol in CH₂Cl₂) afforded a mixture of

- 427 -

diastereoisomers (**256**) as a grey solid (50mg, 82%).
This product (**256**) was used without further
purification (50mg, 0.091mmol) and was hydrogenated in
methanol (5ml) using 10% Pd/carbon (30mg) for 24h. The
5 reaction mixture was filtered and the resulting
solution concentrated. Flash chromatography on silica
gel (2-20% methanol in CH₂Cl₂) afforded compound **257**
(9mg, 21%) as a white solid: ¹H NMR (D⁴-MeOH) δ 7.88-
7.29 (5H, m), 5.18-4.99 (1H, m), 4.59-4.35 (3H, m),
10 4.26-4.11 (1H, m), 3.65-3.41 (2H, m), 3.18-2.91 (1H,
m), 2.62-1.47 (8H, m), 1.29-1.00 (3H, 2d) (mixture of
acetal and hemiacetal). MS (ES -) 457.

- 428 -



Benzyl 3-(N'-benzoylhydrazino)propanoate (259).

Benzylacrylate (1.13ml, 7.34mmol) was added to a stirred suspension of benzoylhydrazine (285) (1.0g, 7.34mmol) in isopropanol (28ml). The mixture was

- 429 -

refluxed for 20h, cooled to room temperature then concentrated. The residue was purified by flash chromatography (20% EtOAc in CH₂Cl₂) to afford **259** (1.098g, 50%) as an oil which crystallized on standing:

5 mp 65 °C; IR (KBr) 3283, 1723, 1644, 1316, 1201, 1156; ¹H NMR (CDCl₃) δ 8.32-8.18 (1H, m), 7.81-7.70 (2H, m), 7.57-7.23 (8H, m), 5.36-4.92 (1H, brm), 5.11 (2H, s), 3.26 (2H, t, *J* = 6.5), 2.59 (2H, t, *J* = 6.5); ¹³C NMR (CDCl₃) δ 172.12, 167.27, 135.65, 132.54, 131.66,

10 128.45, 128.10, 128.06, 126.84, 66.31, 47.33, 33.31; Anal. Calcd for C₁₇H₁₈N₂O₃: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.42; H, 6.10; N, 9.38. MS (ES +) 321 (M + Na, 38%), 299 (M⁺ + 1, 100).

(3S)-1-Benzyl 3-*t*-butyl 2-(N'-benzoyl-N-(2-
 15 benzyloxycarbonylethyl)hydrazinocarbonyl)hexahydro-
 pyridazine-1,3-dicarboxylate (**260**). A solution of
 (3S)-1-benzyl 3-*t*-butyl hexahydropyridazine-1,3-
 dicarboxylate (Hassall et al. J. Chem. Soc. Perkin 1,
 pp. 1451-1454 (1979)) (925.3mg, 2.89mmol) and
 20 diisopropylethylamine (0.70ml, 4.0mmol) in a 1.93M
 toluene solution of phosgene (17.96ml, 34.7mmol) was
 stirred at room temperature for 45min, then
 concentrated to leave a yellow solid. To this solid
 was added toluene (18ml), hydrazide (**259**) (861.6mg,
 25 2.89mmol) and diisopropylethylamine (0.70ml, 4.0mmol).
 The mixture was stirred at room temperature for 2.75h,
 then concentrated. The resulting residue was taken up
 in EtOAc, washed twice with 1M HCl, brine, then dried
 (MgSO₄), filtered and concentrated to afford 2.15g of
 30 crude material. Flash chromatography (40% EtOAc in
 hexane) afforded 1.65g (89%) of the title compound as a
 white foam: mp 40 °C; [α]_D²⁴ -55.78 ° (c 0.40, CH₂Cl₂);

- 430 -

IR (KBr) 3436, 2930, 1733, 1689, 1455, 1412, 1367, 1258, 1156, 697; ^1H NMR (CDCl_3) δ 8.54-8.23 (0.5H, m), 7.97-7.09 (15.5H), 5.16-4.80 (4H, m), 4.66-4.32 (1H, m), 4.24-3.55 (3.3H, m), 3.50-3.26 (0.4H, m), 3.19-2.49 (2.3H, m), 2.11-1.43 (6H, m), 1.32-1.05 (7H, m); Anal. Calcd for $\text{C}_{35}\text{H}_{40}\text{N}_4\text{O}_8 \cdot 0.5\text{H}_2\text{O}$: C, 64.31; H, 6.32; N, 8.57. Found: C, 64.18; H, 6.27; N, 8.56. MS (ES +) 662 (M + Na, 84%), 645 (M^+ + 1, 100), 384 (77).

(6S)-3-(N'benzoyl-N-(6-t-butoxycarbonylhexahydropyridazine-1-carbonyl)hydrazino)propanoic acid (261). A solution of 260 (1.59g, 2.47mmol) in MeOH (142ml) was treated with 10% Palladium on carbon (230.0mg) and stirred under an atmosphere of H_2 for 1.5h. The mixture was filtered and the solvent evaporated to afford 1.04g (100%) of a white foam. This was used in the next step without further purification: mp <40 °C; $[\alpha]_{\text{D}}^{26} +1.6^\circ$ (c 0.26, CH_2Cl_2); IR (KBr) 3422, 2977, 2986, 1728, 1677, 1486, 1445, 1396, 1369, 1309, 1228, 1155, 916, 716; ^1H NMR (CDCl_3) δ 10.0-9.7 (1H, brm), 7.86 (2H, d, $J = 7.5$), 7.62-7.38 (3H, m), 7.3-5.6 (2H, brm), 4.57 (1H, brd, $J = 4.0$), 4.05-3.77 (2H, m), 3.00-2.82 (1H, m), 2.80-2.43 (3H, m), 2.20-2.03 (1H, m), 2.00-1.47 (1H, m), 1.62-1.14 (11H, m); ^{13}C NMR (CDCl_3) δ 175.00, 171.17, 167.62, 160.68, 132.39, 131.77, 128.67, 127.38, 82.27, 54.38, 48.04, 46.35, 33.62, 28.02, 25.68, 21.61. MS (ES +) 443 (M + Na, 68%), 421 (M^+ + 1, 100), 365 (50), 131 (61).

(4S) t-Butyl 7-benzamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262). To a solution of amino acid 261

- 431 -

(1.012g, 2.41mmol) in dry THF (26ml) at 0 °C was added N-ethylmorpholine (597µl, 4.69mmol), followed by PCl₅ (651.3mg, 3.12mmol). The reaction was stirred at 0 °C for 2h, then allowed to warm to rt and stirred for a further 15.5h. The mixture was concentrated and the resulting residue taken up in EtOAc, washed twice with 1M HCl, sat. NaHCO₃, brine, then dried (MgSO₄), filtered and concentrated. Flash chromatography (20% EtOAc in CH₂Cl₂) gave 727.3mg (75%) of the title compound as a white foam: $[\alpha]_D^{26} +51.0^\circ$ (c 0.20, CH₂Cl₂); IR (KBr) 3436, 2979, 1733, 1670, 1483, 1437, 1420, 1299, 1243, 1156; ¹H NMR (CDCl₃) δ 8.70 (1H, s), 7.78 (2H, d, *J* = 7.0), 7.57-7.32 (3H, m), 5.08 (1H, dd, *J* = 2.5, 5.5), 4.59-4.43 (1H, m), 4.08-3.69 (3H, m), 3.07-2.84 (1H, m), 2.57-2.35 (1H, m), 2.34-2.14 (1H, m), 2.07-1.43 (3H, m), 1.48 (9H, s); ¹³C NMR (CDCl₃) δ 172.41, 169.04, 166.35, 158.35, 132.24, 132.03, 128.61, 127.31, 82.77, 55.41, 54.07, 41.57, 32.21, 28.04, 24.97, 20.37; Anal. Calcd for C₂₀H₂₆N₄O₅: C, 59.69; H, 6.51; N, 13.92. Found: C, 59.53; H, 6.53; N, 13.84. MS (ES +) 425 (M + Na, 71%), 403 (M⁺ + 1, 100), 145 (41).

(4S)-7-Benzamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic Acid (263). A solution of ester 262 (720.0mg, 1.80mmol) in a 1:1 mixture of CH₂Cl₂ and TFA (150ml) was stirred for 1.3h under a dry atmosphere. The solution was then reduced in vacuo, taken up in Et₂O and reduced again. This process was repeated six times to afford the crude product as an off-white solid. The product was purified by flash chromatography (5% MeOH in CH₂Cl₂) to afford 520.0mg (83%) of the title compound as a white

- 432 -

foam: $[\alpha]_D^{25} +59.5^\circ$ (c 1.82, CH_2Cl_2); IR (KBr) 3435, 3266, 2956, 1732, 1664, 1524, 1486, 1440, 1302; ^1H NMR (CDCl_3) δ 9.13 (1H, s), 7.77 (2H, d, $J = 7.5$), 7.57-7.32 (3H, m), 5.27-5.16 (1H, m), 4.62-4.43 (1H, m),
 5 4.09-2.70 (3H, m), 3.14-2.89 (1H, m), 2.59-2.43 (1H, m), 2.38-2.20 (1H, m), 2.14-1.89 (1H, m), 1.82-1.59 (2H, m); ^{13}C NMR (CDCl_3) δ 173.65, 172.28, 166.44, 158.42, 132.44, 131.31, 128.61, 127.39, 54.83, 54.01, 42.11, 31.79, 24.42, 20.29; MS (ES $-$) 345 ($\text{M} - \text{H}^+$,
 10 100%), 161 (45).

[2RS,3S(4S)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264).

To a solution of acid 263 (300.0mg, 0.87mmol) and
 15 (2RS,3S)-3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran (Chapman, Bioorg. & Med. Chem. Lett. 2, pp. 615-18 (1992)) (277.6mg, 0.95mmol) in dry CH_2Cl_2 (2.5ml) and dry DMF (2.5ml) at rt was added bis(triphenylphosphine) palladium chloride (13.0mg),
 20 followed by tri-n-butyltin hydride (466.0 μl , 1.73mmol). The reaction was stirred for 5min, then 1-hydroxybenzotriazole (234.1mg, 1.73mmol) was added and the mixture was cooled to 0°C before addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
 25 (204.5mg, 1.04mmol). The mixture was allowed to warm to rt and stirred for 16.5h. The mixture was diluted with EtOAc, washed with 1M NaHSO_4 twice with sat. NaHCO_3 , then H_2O and brine. The organic layer was dried (MgSO_4), filtered and concentrated. The residue
 30 was purified by flash chromatography (5% MeOH in CH_2Cl_2) to afford 358.3mg (77%) of the title compound as a white solid: IR (KBr) 3435, 1791, 1665, 1526,

- 433 -

1421, 1285; ^1H NMR (CDCl_3) δ 8.76 and 8.49 (1H, 2 x s),
7.92-7.73 (2H, m), 7.62-7.24 (8.5H, m), 6.86 (0.5H, d,
 $J = 8.0$), 5.53 and 5.33 (1H, d, $J = 5.5$, s), 4.95-4.34
(5H, m), 4.04-3.54 (3H, m), 3.03-2.64 (2H, m), 2.49-
5 2.14 (2H, m), 2.11-1.46 (4H, m); MS (ES +) 558 (M + Na,
100%), 536 ($\text{M}^+ + 1$, 78), 404 (58).

**[3S(4S)]3-(7-Benzamido-6,10-dioxo-1,2,3,4,7,8,9,10-
octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-
carboxamido)-4-oxobutanoic acid (265).** A mixture of
10 **264** (350.0mg, 0.65mmol), 10% palladium on carbon
(350mg) and methanol (36ml) was stirred under an
atmosphere of H_2 for 6.5h. The mixture was filtered
and the solvent evaporated. Et_2O was added and the
solvent removed again. This process was repeated four
15 times to reveal 283mg (97%) of the title compound, as a
white crystalline solid: mp decarboxylates above
140 °C; $[\alpha]_{\text{D}}^{26} +33.5^\circ$ (c 0.18, MeOH), IR (KBr) 3428,
1663, 1528, 1487, 1437, 1288; ^1H NMR (D_6 -DMSO) δ 10.56
(1H, s), 8.71-8.57 (1H, m), 7.88-7.81 (2H, m), 7.65-
20 7.46 (3H, m), 4.97-4.85 (1H, m), 4.38-4.0 (3H, m),
3.88-3.52 (3H, m), 2.91-2.71 (2H, m), 2.50-2.38 (1H,
m), 2.35-2.21 (1H, m), 2.10-1.94 (1H, m), 1.93-1.49
(3H, m); ^{13}C NMR (D_6 -DMSO) δ 173.66, 172.49, 169.97,
169.89, 164.96, 157.62, 132.35, 131.85, 128.39, 127.32,
25 53.81, 52.69, 40.90, 33.17, 31.60, 24.40, 24.13, 19.24;
MS (ES -).



- 435 -

1530, 1469, 1455, 1392, 1263, 1131, 722; ^1H NMR (CDCl_3) δ 7.83 (2H, m), 7.72 (2H, m), 7.29 (5H, m), 5.41 (1H, m), 5.03 (2H, s), 3.90 (2H, m); MS (ES-), 367 (M - 1).

Sub
A14

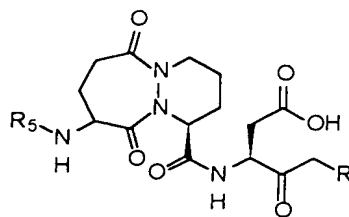
[3S (2S)] t-Butyl 1-benzyloxycarbonyl-2-(3-benzyloxycarbonylamino-2-phthalimidepropionyl)pyridazine-3-carboxylate (267). A suspension of the acid 266 (1.32g, 3.58mmol) in dry ether (37ml) was treated with phosphorus pentachloride (1.04g, 5mmol) and stirred at room temperature for 2h. The solution was filtered to remove unreacted phosphorus pentachloride then evaporated to dryness. The residue was treated with dry toluene (25ml) then evaporated to dryness. This process was repeated several times. The resulting oil was dissolved in dry dichloromethane (25ml), cooled to 0 °C and treated with a solution of (3S) t-butyl 1-benzyloxycarbonylpyridazine-3-carboxylate (1.15g, 3.58mmol) in dry dichloromethane (2ml) followed by 5% aqueous sodium bicarbonate solution (25ml). The mixture was stirred rapidly at room temperature for 20h then diluted with ethyl acetate (100ml) and acidified to pH2 with 1M HCl. The organic phase was washed twice with dilute HCl solution then brine, dried (MgSO_4) and concentrated. The resulting oil was purified by flash chromatography (2-20% ethyl acetate/dichloromethane then 10-20% methanol/dichloromethane) to afford (267), 1.25g (52%) as a white powder: IR (KBr) 3367, 2955, 1722, 1517, 1455, 1387, 1369, 1251, 1153, 721; ^1H NMR (CDCl_3) δ 7.81 (2H, m), 7.74 (2H, m), 7.63 (1H, brs), 7.31 (10H, m), 5.46-4.76 (5H, m), 4.07-3.54 (4H, m), 2.4 (1H, m), 2.0-1.6 (3H, m), 1.40 (9H, s); MS (ES+), 671 (M + 1), 693 (M + Na).

- 436 -

(1*S*,9*S*) *t*-Butyl 1,2,3,4,7,8,9,10-octahydro-10-oxo-9-phthalimido-6*H*-pyridazino[1,2-*a*][1,2,4]triazepine-1-carboxylate (**268**). A solution of ester **267** (50mg, 0.074mmol) in methanol (15ml) was treated with 10% palladium on carbon (50mg) and hydrogenated at room temperature and atmospheric pressure for 24h. The mixture was evacuated thoroughly to remove hydrogen then treated with 37% aqueous formaldehyde (18mg, 0.22mmol) and stirred under nitrogen for 2h. The mixture was filtered, evaporated to dryness and the product purified by flash chromatography (4-100% ethyl acetate/dichloromethane) to afford **268** 14.5mg (48%) as an oil: ¹H NMR (CDCl₃) δ 7.85 (2H, m), 7.71 (2H, m), 5.78 (1H, dd, *J* = 10, 5), 4.99 (1H, dd, *J* = 6.1, 1.5), 4.07 (1H, d, *J* = 10.6), 3.49 (1H, dd, *J* = 14, 5), 3.39 (1H, d, *J* = 10.3), 3.24 (1H, dd, *J* = 14, 10.2), 3.17 (2H, m), 2.39 (1H, m), 1.84-1.46 (3H), 1.51 (9H, s); MS (ES⁺), 415 (*M* + 1), 437 (*M* + Na).

Compounds **280-283** were prepared from **212b** by a method similar to the method used to prepare **226e**. Compounds **284-287** were prepared by a method similar to the method used to prepare **217e**.

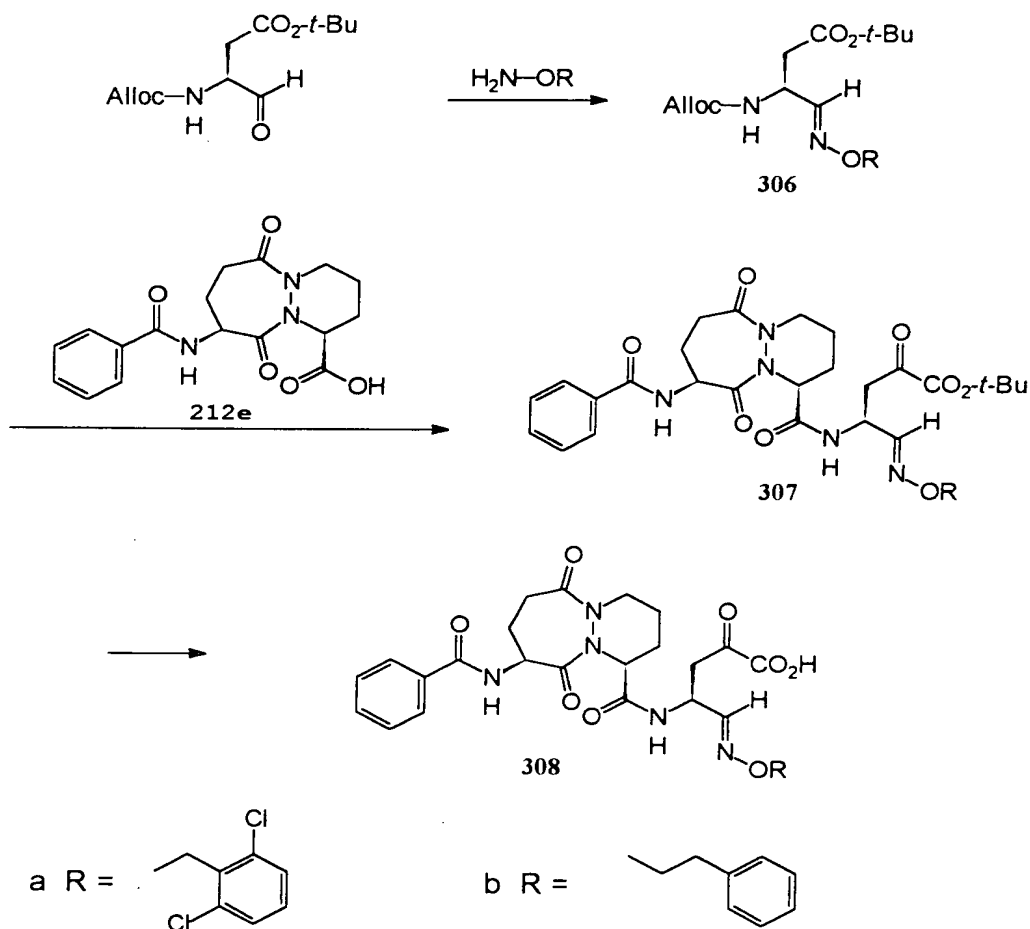
- 437 -



280-287

compound	R ₅	R
280		
281		
282		
283		
284		
285		
286		
287		

- 438 -



(3S) 3-Allyloxycarbonylamino-4-oxobutyric acid tert-butyl ester O-(2,6-dichlorophenylmethyl)oxime (306a) was prepared by a similar procedure as 208a except that 2,6-dichlorophenylmethoxyamine (prepared by a similar method as 306b) was used instead of semicarbazide to give 870mg (quant.) as a clear oil.

(3S) 3-Allyloxycarbonylamino-4-oxobutyric acid tert-butyl ester O-(2-(phenyl)ethyl)oxime (306b) was prepared by a similar procedure as 208a except that 2-

- 439 -

(phenyl)ethoxyamine (US 5 346 911) was used instead of semicarbazide to give 395mg (quant.) as a clear oil.

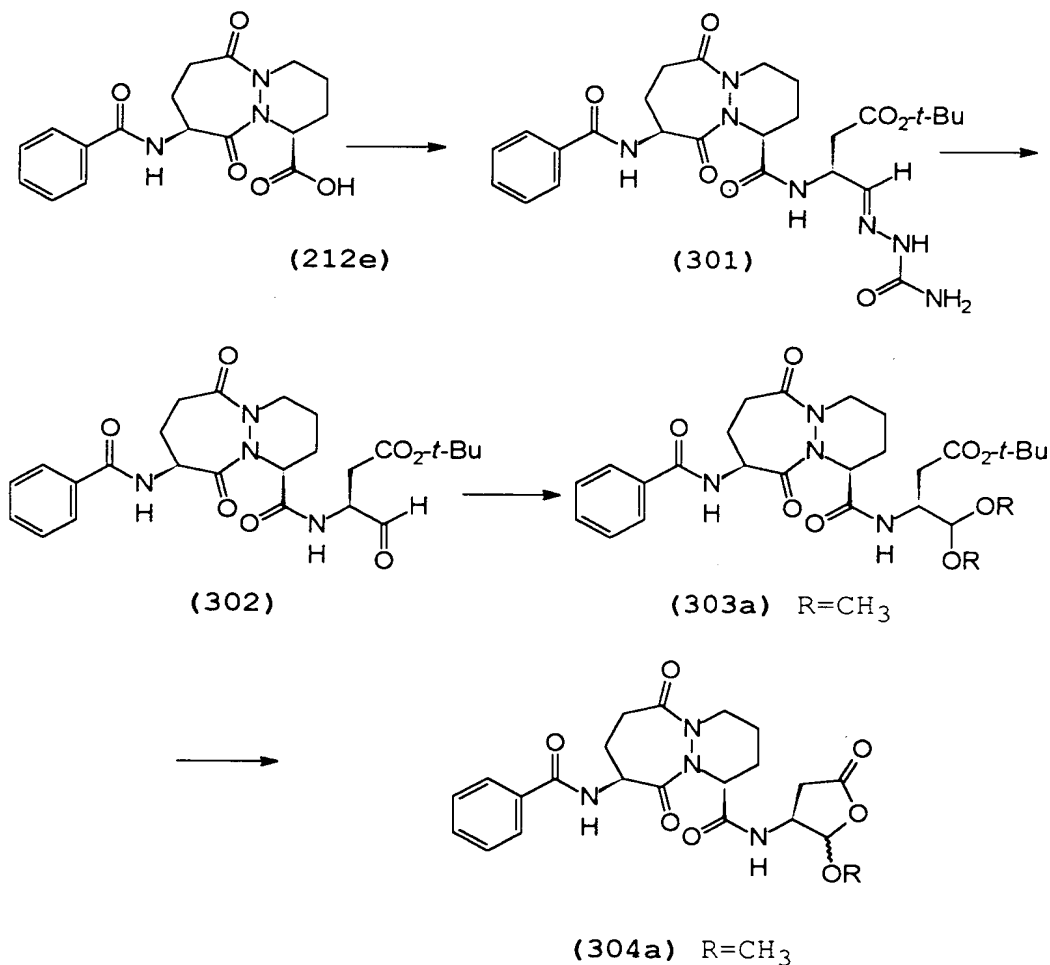
5 [3*S*(1*S*,9*S*) 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-*a*][1,2]diazapine-1-carboxamido)-amino]-4-oxobutanoic acid t-butyl ester, O-(2,6-dichlorophenylmethyl)oxime (307a) was prepared by a procedure similar to 233e except 306a was used instead of 207a to give 23 mg(23%) of 307a as a white solid.

10 [3*S*(1*S*,9*S*) 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-*a*][1,2]diazapine-1-carboxamido)-amino]-4-oxobutanoic acid t-butyl ester, O-(2-(phenyl)ethyl)oxime (307b) was prepared by a procedure
15 similar to 233e except 306b was used instead of 207a to give 43 mg(48%) of 307b as a white solid.

[3*S*(1*S*,9*S*) 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-*a*][1,2]diazapine-1-carboxamido)-amino]-4-oxobutanoic acid, O-(2,6-dichlorophenylmethyl)oxime
20 (308a) was prepared by from 307a a procedure similar to the preparation of 235e from 234e to give 15.2 mg (74%) as white solid: ¹H NMR(CD₃OD) δ 0.9(m), 1.3(s), 1.7(m), 1.8(m), 2.0(m), 2.1-2.2(m), 2.3(dd), 2.4-
25 2.5(m), 2.6(m), 2.7-2.8(m), 3.1(m), 3.3(m), 3.4-3.5(m), 4.5(m), 4.9(m), 5.1(m), 5.3(d), 5.4(s), 6.8(d), 7.2-7.5(m), 7.8(dd), 8.4(dd).

- 440 -

[3*S*(1*S*,9*S*) 3-(9-Benzoylamino-6,10-dioxo-
 1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino-
 [1,2-*a*][1,2]diazapine-1-carboxamido)-amino]-4-
 oxobutanoic acid, *O*-(2-(phenyl)ethyl)oxime (308b) was
 5 prepared by from 307b a procedure similar to the
 preparation of 235e from 234e to give 25.2 mg (68%) as
 white solid: ^1H NMR(CD₃OD) δ 1.2(m), 1.6-1.7(m), 2.0-
 2.1(m), 2.2(m), 2.3(m), 2.5(m), 2.6-2.7(dd), 2.9(t),
 3.0(t), 3.1(m), 3.3-3.5(m), 4.2(t), 4.25(m), 4.5(m),
 10 5.2(t), 5.3(t), 6.7(d), 7.1-7.2(m), 7.35(dd), 7.4(m),
 7.5(m), 7.8(dd), 8.3(dd).



- 441 -

[3*S*(1*S*,9*S*) 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyriazino-[1,2-*a*][1,2]diazapine-1-carboxamido)-amino]-4-oxobutanoic acid *tert*-butyl ester (302).

5 **Step A:** 301 was prepared by procedure similar to 605a (Step A), except 212e was used instead of 603a to give 540 mg (34%) to give a white solid.

Step B: 302. A solution of 301 (50.7 mg; 0.091 mmol) in 2.8 ml of MeOH/HOAc/37% aq. formaldehyde (5:1:1) was
10 stirred at rt for 5.5 h. and the reaction was concentrated to 0.7 ml *in vacuo*. The residue was dissolved in 3 ml of CH₃CN and concentrated to 0.7 ml (3x), dissolved in toluene and concentrated to 0.7 ml *in vacuo* (2x), and concentrated to dryness.
15 Chromatography (flash, SiO₂, 5% isopropanol/CH₂Cl₂) gave 302 (45.5 mg, 78%) as a white solid: ¹H NMR(DMSO-*d*₆) δ 1.0-1.15(m, 2H), 1.4(s, 9H), 1.65(m, 2H), 1.9-2.1(m, 2H), 2.15-2.4(m, 3H), 2.55(m, 1H), 2.7-3.0(m, 2H), 4.3-4.6(m, 2H), 4.9(m, 1H), 5.2(m, 1H), 7.4-7.6(m, 2H),
20 7.8-8.0(m, 2H), 8.6(m, 1H), 8.8(m, 1H), 9.4(s, 1H).

[1*S*,9*S* (2*RS*,3*S*)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-*N*-(2-methoxy-5-oxo-tetrahydro-furan-3-yl)-6*H*-pyridazino[1,2-*a*][1,2]diazapine-1-carboxamide. (304a).

25 **Step A:** A solution of 302 (90 mg; 0.18 mmol) in 10 ml of MeOH was treated with trimethylorthoformate (1ml) and *p*-toluene sulfonic acid hydrate (5 mg; 0.026 mmol) and the reaction was stirred for 20 h. The reaction was treated with 3 ml of aq. sat. NaHCO₃ and
30 concentrated *in vacuo*. The residue was taken up in

- 442 -

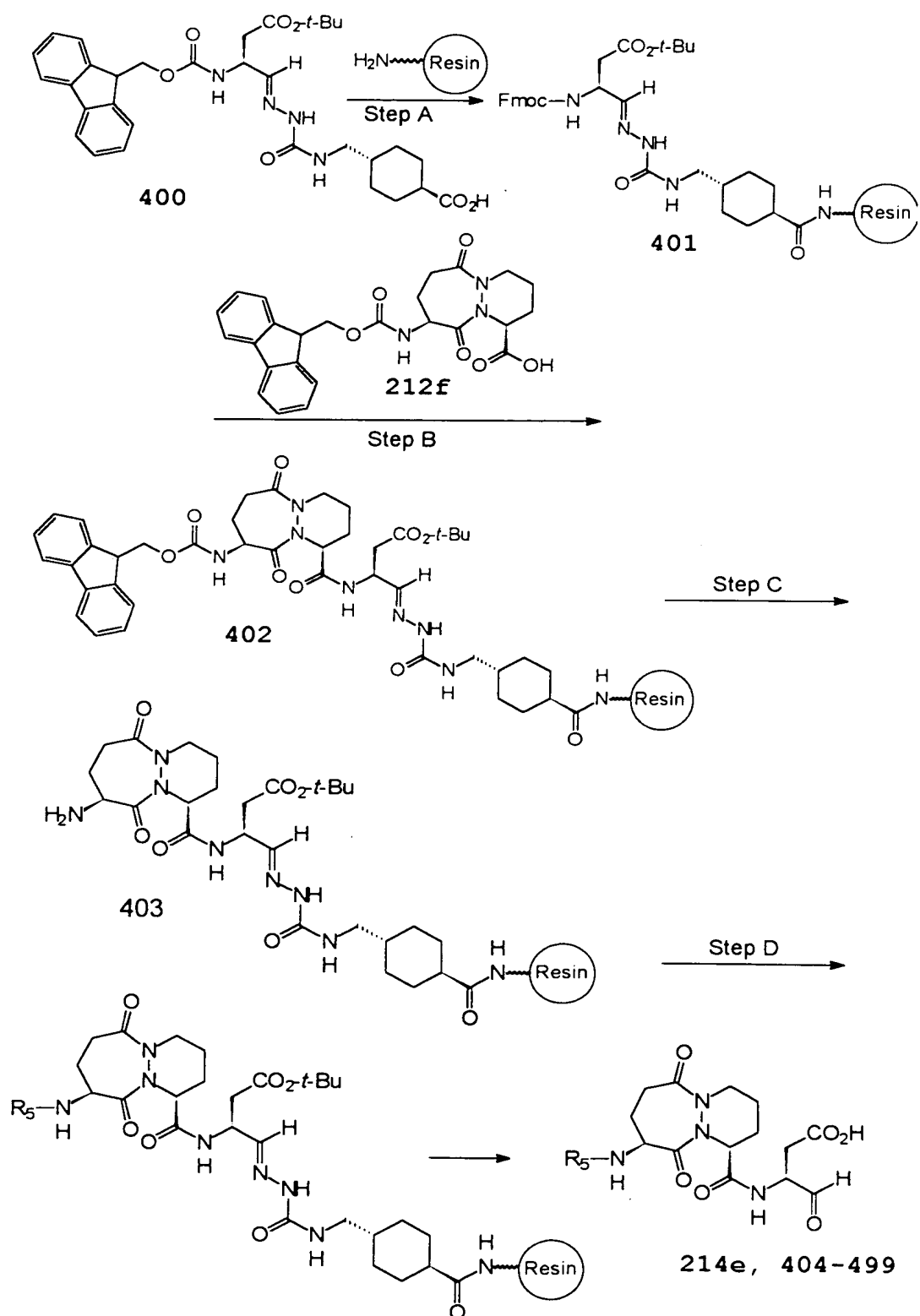
EtOAc and washed with dilute aq. NaHCO_3 , dried over MgSO_4 and concentrated *in vacuo* to give 80 mg of **303a**.

Step B: **303a** was dissolved in 2 ml of TFA and stirred at rt for 15 min. The reaction was dissolved in CH_2Cl_2 and concentrated *in vacuo* (3x). Chromatography (flash, SiO_2 , 1% to 3% MeOH/ CH_2Cl_2 gave 43 mg (64%) of **304a** as a white solid: ^1H NMR(CDCl_3) δ 1.55-1.8(m, 2H), 1.9-2.15(m, 4H), 2.25-2.5(m, 2H), 2.7-3.3(m, 4H), 3.45, 3.6(s, s, 3H), 4.4, 4.75(2m, 1H), 4.6(m, 1H), 4.95, 5.4(t,d, 1H), 5.1-5.2(m, 1H), 6.45, 7.05(2d, 1H), 6.95(m, 1H), 7.45(m, 2H), 7.5(m, 1H), 7.85(m, 2H).

Example 11

Compounds **214e**, **404-413**, **415-445**, **446-468**, **470-491**, and **493-499** were synthesized as described in Example 11 and Table 7.

- 443 -



- 444 -

Step A. Synthesis of 401. TentaGel S[®] NH₂ resin (0.16 mmol/g, 10.0 g) was placed in a sintered glass funnel and washed with DMF (3 x 50 mL), 10% (v/v) DIEA in DMF (2 x 50 mL) and finally with DMF (4 x 50 mL).
5 Sufficient DMF was added to the resin to obtain a slurry followed by **400** (1.42 g, 2.4 mmol, prepared from (3S)-3-(fluorenylmethyloxycarbonyl)-4-oxobutryic acid t-butyl ester according to A.M. Murphy et. al. J. Am. Chem. Soc., 114, 3156-3157 (1992)), 1-
10 hydroxybenzotriazole hydrate (HOBT·H₂O; 0.367 g, 2.4 mmol), O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU; 0.91 g, 2.4 mmol), and DIEA (0.55 mL, 3.2 mmol). The reaction mixture was agitated overnight at rt using a wrist arm shaker. The resin
15 was isolated on a sintered glass funnel by suction filtration and washed with DMF (3 x 50 mL). Unreacted amine groups were then capped by reacting the resin with 20% (v/v) Ac₂O/DMF (2 x 25 mL) directly in the funnel (10 min/wash). The resin was washed with DMF (3
20 x 50 mL) and CH₂Cl₂ (3 x 50 mL) prior to drying overnight *in vacuo* to yield **401** (11.0 g, quantitative yield).

Step B. Synthesis of 402. Resin **401** (6.0 g, 0.16 mmol/g, 0.96 mmol) was swelled in a sintered glass
25 funnel by washing with DMF (3 x 25 mL). The Fmoc protecting group was then cleaved with 25% (v/v) piperidine/DMF (25 mL) for 10 min (intermittent stirring) and then for 20 min with fresh piperidine reagent (25 mL). The resin was then washed with DMF (3
30 x 25 mL), followed by N-methylpyrrolidone (2 x 25 mL). After transferring the resin to a 100 mL flask, N-methylpyrrolidone was added to obtain a slurry followed

- 445 -

by **212f** (0.725 g, 1.57 mmol), HOBT·H₂O (0.25 g, 1.6 mmol), HBTU (0.61 g, 1.6 mmol) and DIEA (0.84 mL, 4.8 mmol). The reaction mixture was agitated overnight at rt using a wrist arm shaker. The resin work-up and
5 capping with 20% (v/v) Ac₂O in DMF were performed as described for **401** to yield **402** (6.21 g, quantitative yield).

Step C. Synthesis of 403. This compound was prepared from resin **402** (0.24 g, 0.038 mmol) using an
10 Advanced ChemTech 396 Multiple Peptide synthesizer. The automated cycles consisted of a resin wash with DMF (3 x 1 mL), deprotection with 25% (v/v) piperidine in DMF (1 mL) for 3 min followed by fresh reagent (1 mL) for 10 min to yield resin **403**. The resin was washed
15 with DMF (3 x 1 mL) and *N*-methypyrrolidone (3 x 1 mL).

Step D. Method 1. [**3S(1S,9S)**]-3-(6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-9-(thiophene-3-carbonylamino)-6*H*-pyridazine[1,2-*a*][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (**409**). Resin **403** was
20 acylated with a solution of 0.4M thiophene-3-carboxylic acid and 0.4M HOBT in *N*-methypyrrolidone (1 mL), a solution of 0.4M HBTU in *N*-methypyrrolidone (0.5 mL) and a solution of 1.6M DIEA in *N*-methypyrrolidone (0.35 mL) and the reaction was shaken for 2 hr at rt. The
25 acylation step was repeated. Finally, the resin was washed with DMF (3 x 1 mL), CH₂Cl₂ (3 x 1 mL) and dried *in vacuo*. The aldehyde was cleaved from the resin and globally deprotected by treatment with 95% TFA/5% H₂O (v/v, 1.5 mL) for 30 min at rt. After washing the
30 resin with cleavage reagent (1 mL), the combined filtrates were added to cold 1:1 Et₂O:pentane (12 mL)

- 446 -

and the resulting precipitate was isolated by centrifugation and decantation. The resulting pellet was dissolved in 10% CH₃CN/90% H₂O/0.1% TFA (15 mL) and lyophilized to obtain crude **409** as a white powder. The
5 compound was purified by semi-prep RP-HPLC with a Rainin Microsorb™ C18 column (5 μ, 21.4 x 250 mm) eluting with a linear CH₃CN gradient (5% - 45%) containing 0.1% TFA (v/v) over 45 min at 12 mL/min. Fractions containing the desired product were pooled
10 and lyophilized to provide **409** (10.8 mg, 63%).

Step D. Method 1A. Synthesis of 418. Following a similar procedure as method 1, resin **403** was acylated with 4-(1-fluorenylmethoxycarbonylamino)benzoic acid and repeated. The Fmoc group was removed as described
15 in Step C and the free amine was acetylated with 20% (v/v) Ac₂O in DMF (1 mL) and 1.6M DIEA in *N*-methylpyrrolidone (0.35 mL) for 2 hr at rt. The acetylation step was repeated. Cleavage of the aldehyde from the resin gave **418** (3.2 mg).

20 **Step D. Method 1B. Synthesis of 447.** Following a similar procedure as method 1A, resin **403** was acylated with 0.4M 4-(1-fluorenylmethoxycarbonylamino)benzoic acid. The acylation step was repeated once. The Fmoc group was
25 removed as before and the free amine was reacted with 1M methanesulfonyl chloride in CH₂Cl₂ (0.5 mL) and 1M pyridine in CH₂Cl₂ (0.60 mL) for 4 hr at rt. Cleavage of the aldehyde from the resin gave **447** (10.0 mg).

Step D. Method 2. Synthesis of 214e. Following
30 a similar procedure as method 1, resin **403** was acylated

- 447 -

with 0.5M benzoyl chloride in *N*-methypyrrolidone (1 mL) and 1.6M DIEA in *N*-methypyrrolidone (0.35 mL) for 2 hr at rt. The acylation step was repeated. Cleavage of the aldehyde from the resin gave **214e** (5.1 mg, 30%).

5 **Step D. Method 3. Synthesis of 427.** Following a similar procedure as method 1, resin **403** was reacted with 1.0M benzenesulfonyl chloride in CH₂Cl₂ (0.5 mL) and 1M pyridine in CH₂Cl₂ (0.60 mL) for 4 hr at rt. The reaction was repeated. Cleavage of the aldehyde
10 from the resin gave **427** (7.2 mg, 40%).

Step D. Method 4. Synthesis of 420. Following a similar procedure as method 1, resin **403** was reacted with 0.5M methylisocyanate in *N*-methypyrrolidone (1 mL) and 1.6M DIEA in *N*-methypyrrolidone (0.35 mL) for 2
15 hr at rt. The reaction was repeated. Cleavage of the aldehyde from the resin gave **420** (8.3 mg, 55%).

Step D. Method 5. Synthesis of 445. Following a similar procedure at method 1, resin **403** was acylated with 0.27M imidazole-2-carboxylic acid (1 mL) in 2:1
20 DMF:H₂O (with 1 eq. DIEA) and 1M 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) in 2:1 *N*-methypyrrolidone/H₂O (0.35 mL) for 3 hr at rt. Cleavage of the aldehyde from the resin gave
445 (9.5 mg).

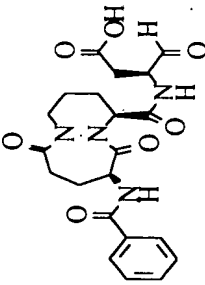
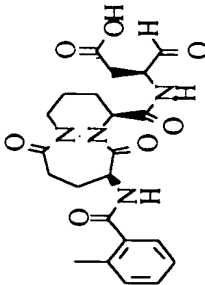
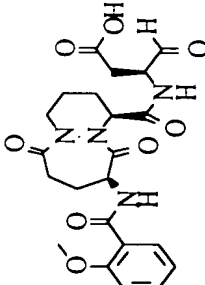
25 **Analytical HPLC methods:**

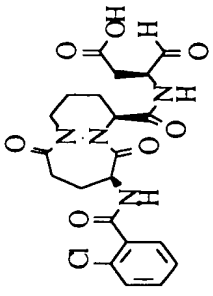
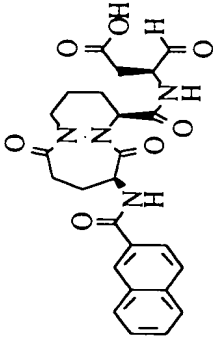
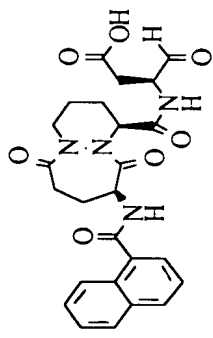
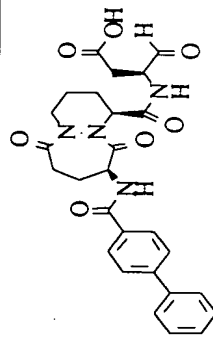
(1) Waters DeltaPak C18, 300A (5μ, 3.9 x 150 mm).
Linear CH₃CN gradient (5% - 45%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.

- 448 -

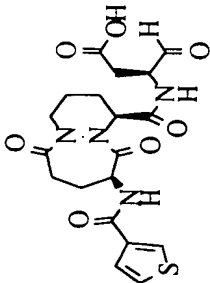
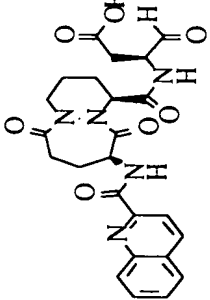
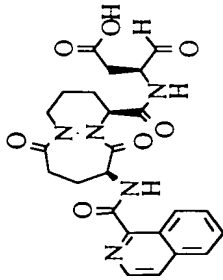
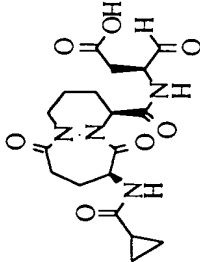
- (2) Waters DeltaPak C18, 300A (5 μ , 3.9 x 150 mm).
Linear CH₃CN gradient (0% - 25%) containing 0.1% TFA
(v/v) over 14 min at 1 mL/min.
- (3) Waters DeltaPak C18, 300A (5 μ , 3.9 x 150 mm).
5 Isocratic elution with 0.1% TFA/water (v/v) at 1
mL/min.
- (4) Waters DeltaPak C18, 300A (5 μ , 3.9 x 150 mm).
Linear CH₃CN gradient (0% - 30%) containing 0.1% TFA
(v/v) over 14 min at 1 mL/min.
- 10 (5) Waters DeltaPak C18, 300A (5 μ , 3.9 x 150 mm).
Linear CH₃CN gradient (0% - 35%) containing 0.1% TFA
(v/v) over 14 min at 1 mL/min.

Table 7

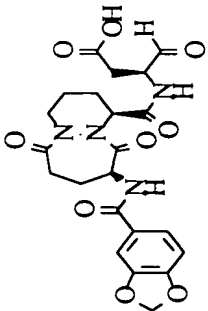
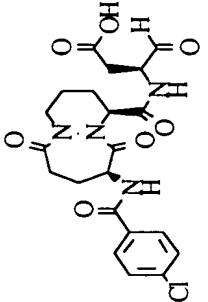
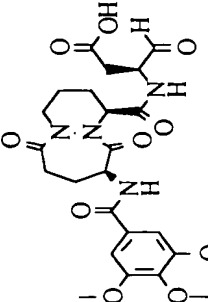
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) ⁺	Syn. Method
214e		C21H24N4O7	444.45	6.67 (2) 98%	445	2
404		C22H26N4O7	458.48	6.66 (2) 97%	459	2
405		C22H26N4O8	474.47	8.2 (1) 98%	475	2

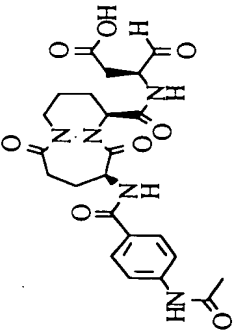
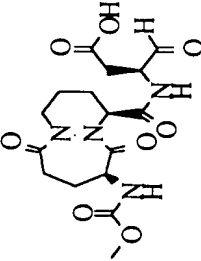
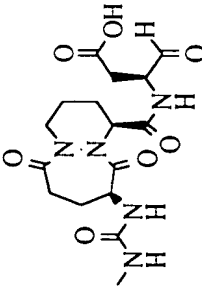
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) ⁺	Syn. Method
406		C21H23ClN4O7	478.89	6.33 (1) 98%	479	2
407		C25H26N4O7	494.51	9.90 (1) 98%	495	2
408		C25H26N4O7	494.51	9.0 (1) 98%	495	2
409		C27H28N4O7	520.55	11.14 (1) 98%	521	2

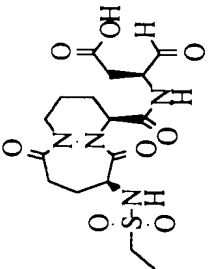
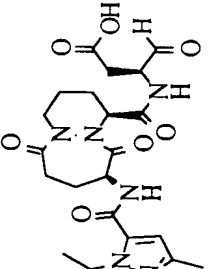
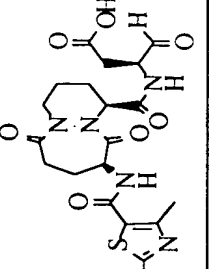
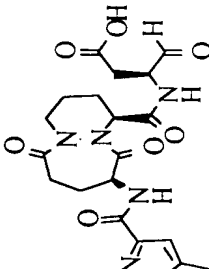
- 451 -

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) ⁺	Syn. Method
410		C19H22N4O7S	450.47	4.87 (1) 98%	451	1
411		C24H25N5O7	495.50	10.7 (1) 98%	496	1
412		C24H25N5O7	495.50	8.57 (1) 98%	496	1
413		C18H24N4O7	408.41	7.21 (2) 98%	409	1

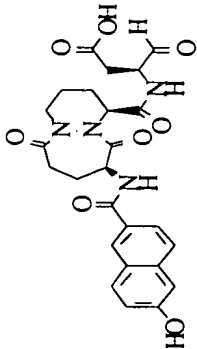
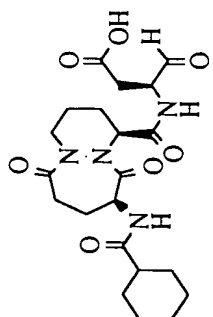
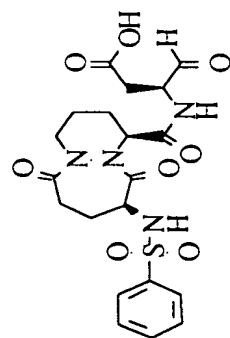
- 452 -

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) ⁺	Syn. Method
415		C22H24N4O9	488.46	7.58 (1) 98%	489	1
416		C21H23ClN4O7	478.89	9.66 (1) 98%	479	1
417		C24H30N4O10	534.53	8.12 (1) 535	535	1

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) ⁺	Syn. Method
418		C23H27N5O8	501.50	5.93 (1) 98%	502	1A
419		C16H22N4O8	398.38	6.84 (2) 98%	399	2
420		C16H23N5O7	397.39	5.25 (2) 98%	398	4

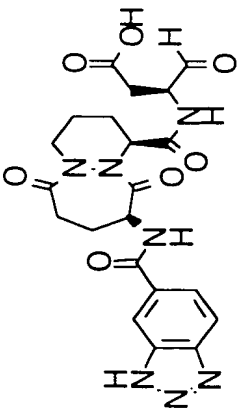
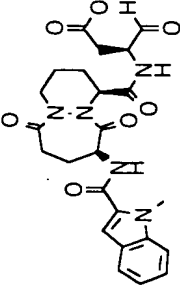
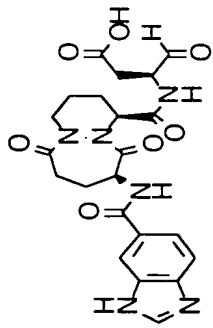
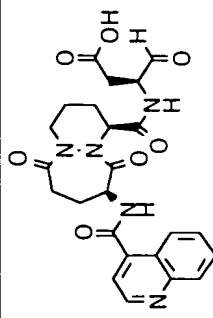
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
421		C16H24N4O8S	432.46	7.13 (2) 98%	433	3
422		C21H28N6O7	476.49	6.89 (1) 98%	477	1
423		C20H25N5O7S	479.52	5.62 (1) 98%	480	1
424		C19H23N5O8	449.42	6.28 (1) 450	450	1

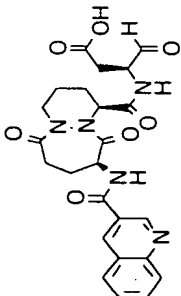
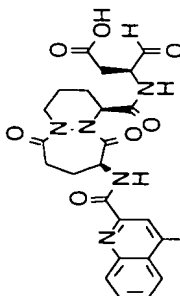
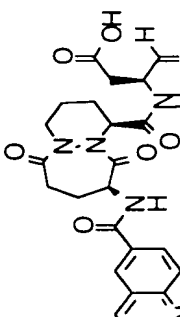
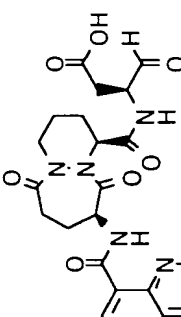
- 455 -

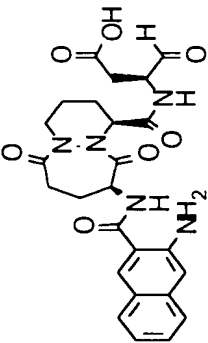
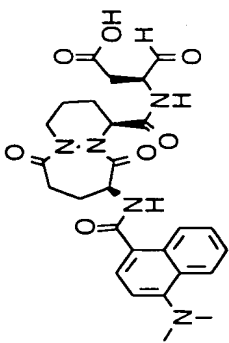
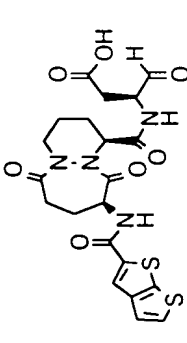
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
425		C25H26N4O8	510.51	8.25 (1) 98%	511	1
426		C21H30N4O7	450.50	8.0 (1) 98%	451	2
427		C20H24N4O8S	480.50	7.87 (1) 98%	481	3

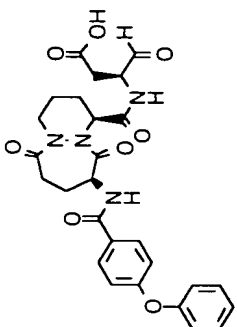
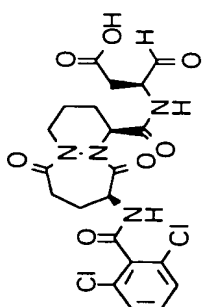
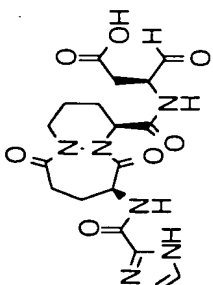
- 456 -

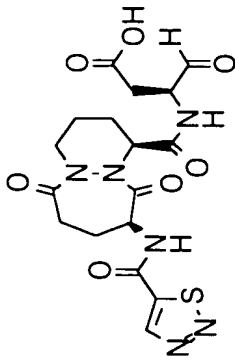
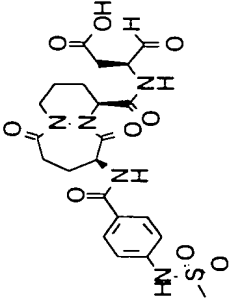
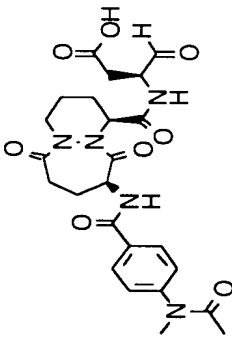
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) ⁺	Syn. Method
428		C16H25N5O8S	447.47	5.13 (1) 98%	448	3
429		C14H20N4O6	340.34	3.19 (3) 98%	341	
430		C23H27N5O8	501.50	5.53 (1) 98%	502	1A
431		C21H25N5O7	459.46	6.66 (2) 98%	460	1

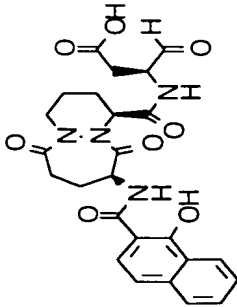
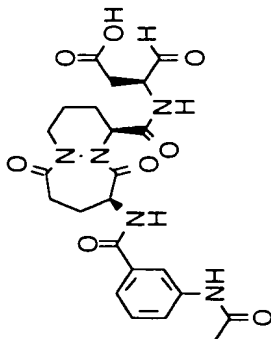
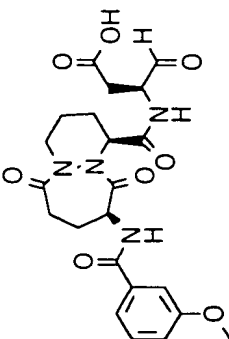
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) ⁺	Syn. Method
432		C21H23N7O7	485.46	5.59 (1) 98%	486	1
433		C24H27N5O7	497.51	11.07 (1) 97%	498	1
434		C22H24N6O7	484.47	4.43 (1) 98%	485	1
435		C24H25N5O7	495.50	5.10 (1) 98%	496	1

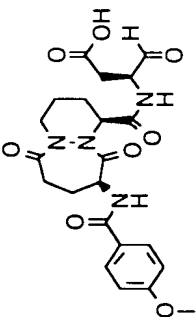
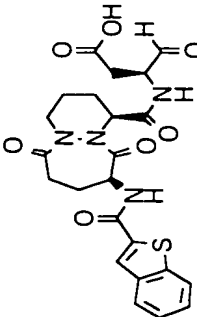
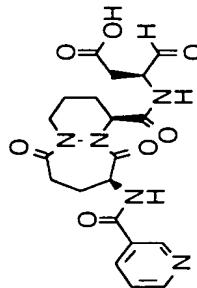
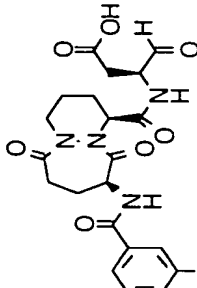
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
436		C24H25N5O7	495.50	8.20 (4) 98%	496	1
437		C25H27N5O8	525.52	12.78 (5) 98%	526	1
438		C24H25N5O7	495.50	4.85 (1) 98%	496	1
439		C24H25N5O7	495.50	8.70 (5) 98%	496	1

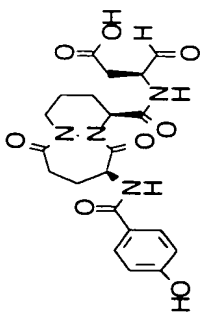
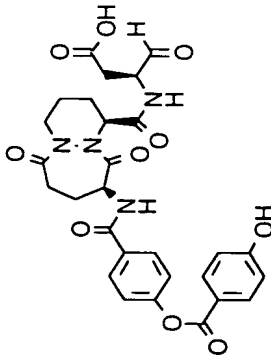
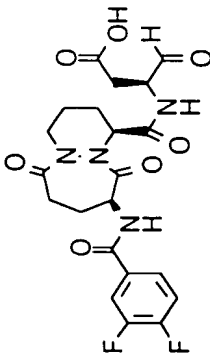
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) ⁺	Syn. Method
440		C25H27N5O7	509.52	9.96 (5) 98%	510	1
441		C27H31N5O7	537.58	6.15 (1) 98%	538	1
442		C21H22N4O7S2	506.56	10.10 (1) 98%	507	1

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
443		C27H28N4O8	536.55	13.12 (1) 98%	537	1
444		C21H22Cl2N4O7	513.34	9.96 (5) 98%	510	1
445		C18H22N6O7	434.41	5.72 (1) 98%	435	5

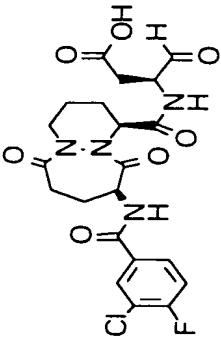
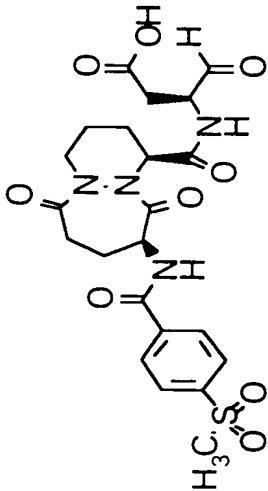
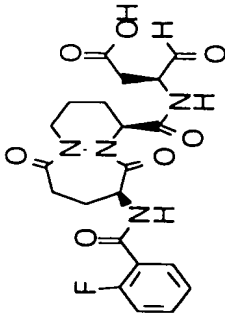
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) ⁺	Syn. Method
446		C17H20N6O7S	452.45	5.00 (1) 98%	453	1
447		C22H27N5O9S	537.55	6.32 (1) 98%	538	1B
448		C24H29N5O8	515.53	6.36 (1) 98%	516	1A

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
449		C25H26N4O8	510.51	13.86 (1) 98%	511	1
450		C23H27N5O8	501.50	6.10 (1) 98%	502	1A
451		C22H26N4O8	474.47	8.02 (1) 98%	475	2

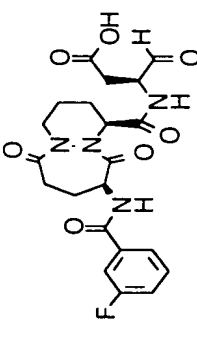
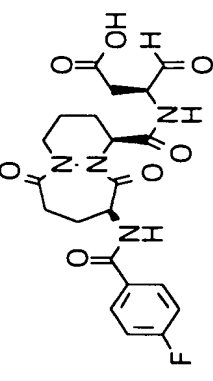
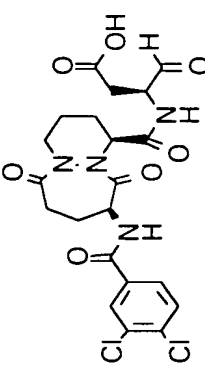
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
452		C22H26N4O8	474.47	7.77 (1) 98%	475	2
453		C23H24N4O7S	500.53	11.11 (1) 98%	501	2
454		C20H23N5O7	445.44	6.24 (2) 98%	446	2
455		C21H23ClN4O7	478.89	9.45 (1) 98%	479	2

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
456		C ₂₁ H ₂₄ N ₄ O ₈	460.45	5.58 (1) 98%	(M+Na) 483	1
457		C ₂₈ H ₂₈ N ₄ O ₁₀	580.56	10.42 (1) 98%	(M+Na) 603	1
458		C ₂₁ H ₂₂ F ₂ N ₄ O ₇	480.43	8.65 (1) 98%	481.1	1

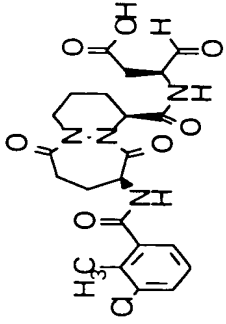
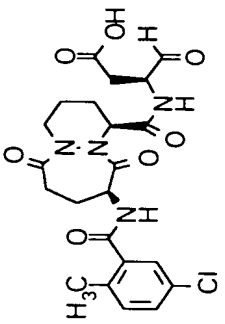
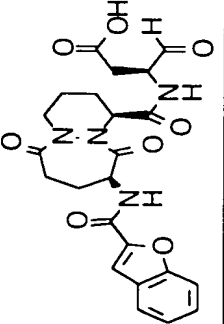
- 465 -

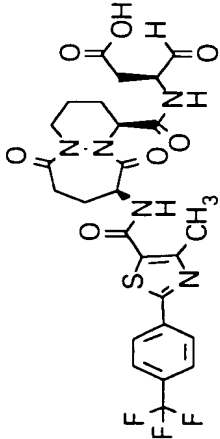
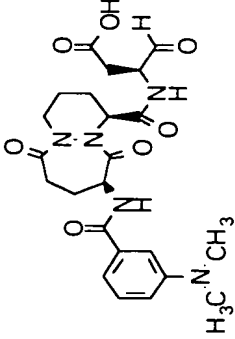
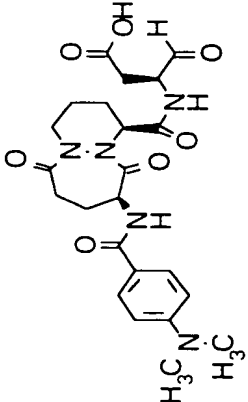
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
459		C21H22ClFN4O7	496.88	10.11 (1) 98%	498.3	1
460		C22H26N4O9S	522.54	6.16 (1) 98%	523.6	1
461		C21H23FN4O7	462.44	7.41 (1) 98%	463.3	1

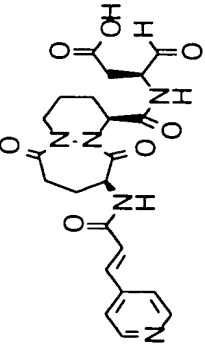
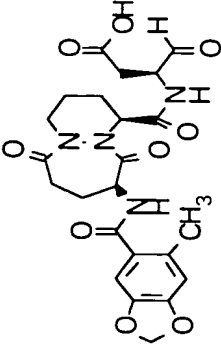
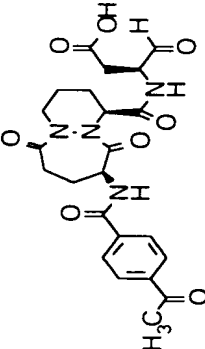
- 466 -

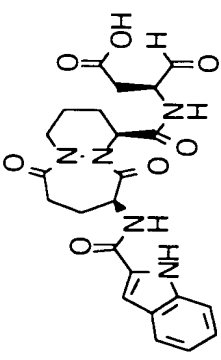
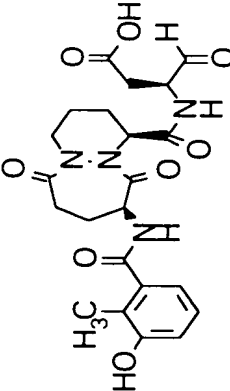
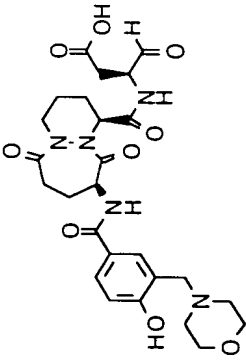
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
462		C21H23FN4O7	462.44	7.71 (1) 98%	463.3	1
463		C21H23FN4O7	462.44	7.64 (1) 98%	464	1
464		C21H22Cl2N4O7	513.34	11.59 (1) 98%	414.5	1

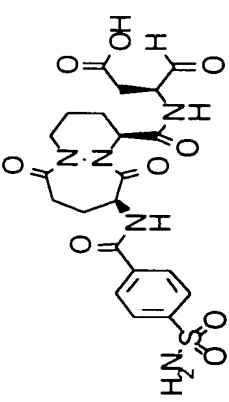
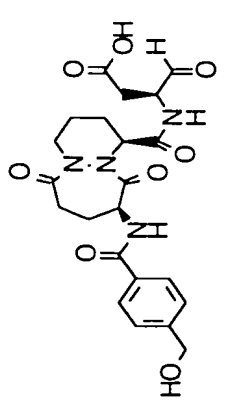
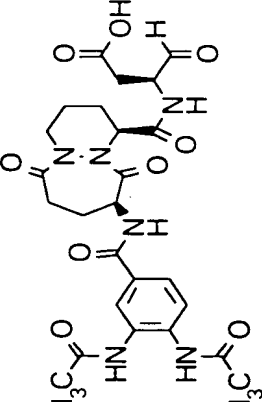
- 467 -

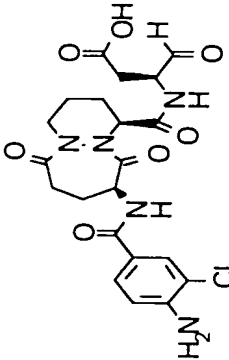
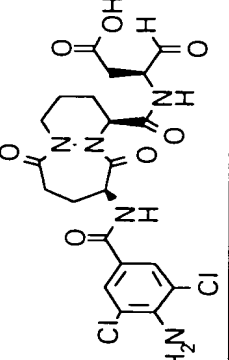
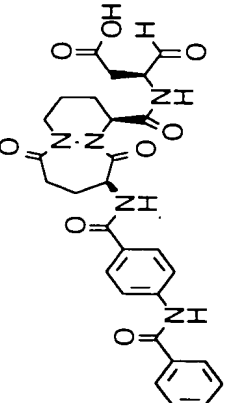
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
465		C22H25ClN4O7	492.92	9.65 (1) 98%	493.9	1
466		C22H25ClN4O7	492.92	9.63 (1) 98%	493.9	1
467		C23H24N4O8	484.47	9.73 (1) 98%	485.8	1

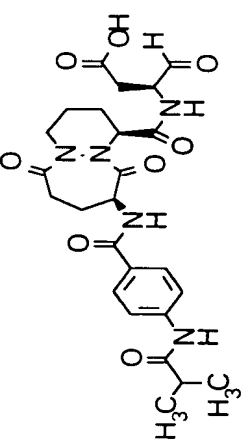
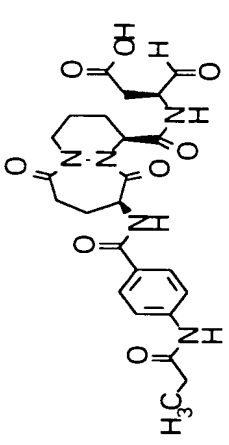
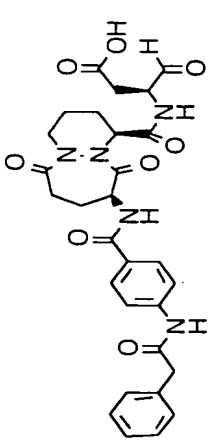
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) ⁺	Syn. Method
468		C26H26F3N5O7S	609.59	14.84 (1) 98%	609.7	1
470		C23H29N5O7	487.52	4.57 (1) 98%	489.5	1
471		C23H29N5O7	487.52	5.74 (1) 98%	488.2	1

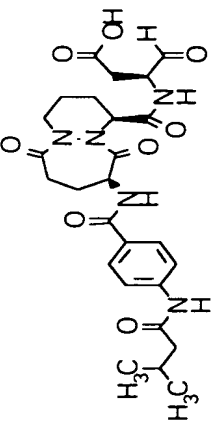
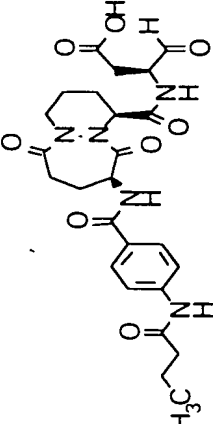
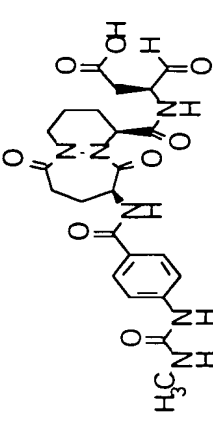
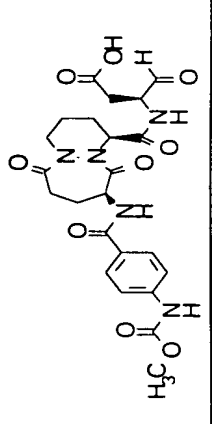
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
472		C22H25N5O7	471.47	4.00 (1) 98%	474	1
473		C23H26N4O9	502.49	7.65 (1) 98%	503.6	1
474		C23H26N4O8	486.49	7.16 (1) 98%	488.1	1

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) ⁺	Syn. Method
475		C23H25N5O7	483.49	9.77 (1) 97%	485.1	1
476		C22H26N4O8	474.47	5.25 (1) 98%	475.8	1
477		C26H33N5O9	559.58	4.76 (1) 95%	561.8	1

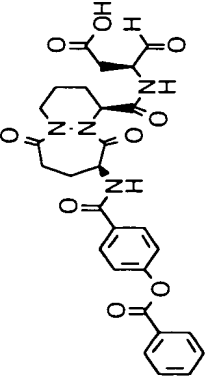
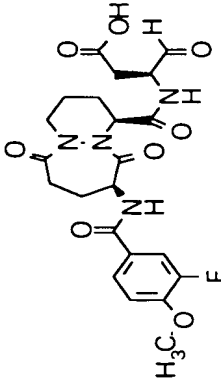
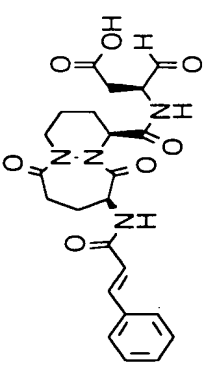
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
478		C21H25N5O9S	523.53	5.25 (1) 98%	524.3	1
479		C22H26N4O8	474.47	5.35 (1) 98%	475.8	1
480		C25H30N6O9	558.55	5.11 (1) 98%	559.3	1A

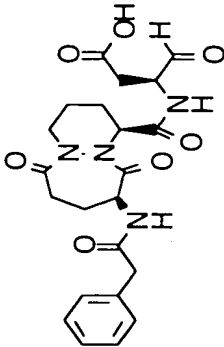
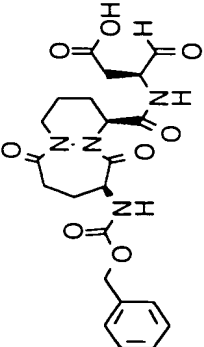
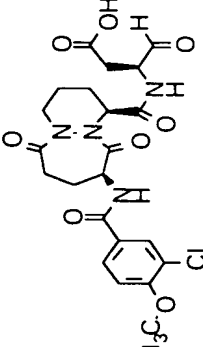
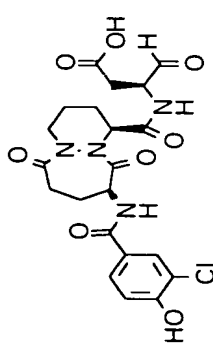
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) ⁺	Syn. Method
481		C21H24ClN5O7	493.9	7.10 (1) 98%	495.1	1
482		C21H23Cl2N5O7	528.4	9.05 (1) 98%	529.8	1
483		C28H29N5O8	563.57	10.01 (1) 98%	565.6	1,2

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) ⁺	Syn. Method
484		C25H31N5O8	529.55	7.88 (1) 98%	531	1,2
485		C24H29N5O8	515.53	7.00 (1) 98%	517.6	1,2
486		C29H31N5O8	577.60	10.43 (1) 98%	579.4	1,2

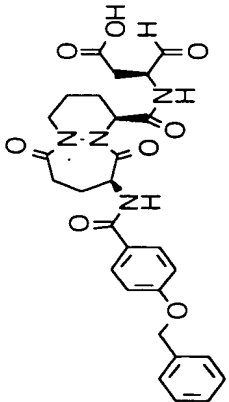
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
487		C26H33N5O8	543.58	9.30 (1) 98%	545.7	1,2
488		C25H31N5O8	529.55	8.13 (1) 98%	531.1	1,2
489		C23H28N6O8	516.52	5.89 (1) 98%	517.8	1,4
490		C23H27N5O9	517.50	7.27 (1) 98%	(M+Na) 540.8	1,2

- 475 -

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) ⁺	Syn. Method
491		C28H28N4O9	564.56	12.9 (1) 98%	565.3	1
493		C22H25FN4O8	492.46	8.31 (1) 98%	493.9	1
494		C23H26N4O7	470.49	9.34 (1) 98%	471.2	2

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) ⁺	Syn. Method
495		C22H26N4O7	458.48	7.24 (1) 98%	459.9	2
496		C22H26N4O8	474.47	9.47 (1) 98%	475.7	2
497		C22H25ClN4O8	508.92	9.58 (1) 98%	509.5	1
498		C21H23ClN4O8	494.89	7.18 (1) 98%	495.1	1

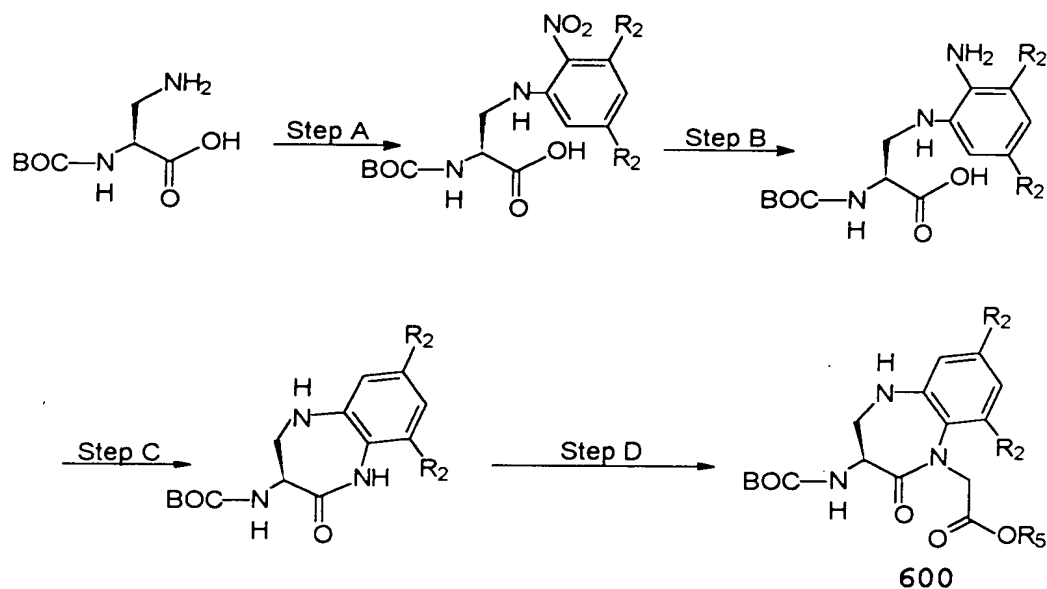
- 477 -

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) ⁺	Syn. Method
499		C28H30N4O8	550.57	13.27 (1) 98%	552	1

- 478 -

Example 12

Compounds 605a-j, 605m-q, 605s, 605t, and 605v were synthesized as described below.



Compound no.	R ₂	R ₅
600a/103	H	CH ₃
600b	H	CH ₂ Ph
600c	CH ₃	CH ₂ Ph

(3*S*)-2-Oxo-3-*tert*-butoxycarbonylamino-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid methyl ester (600a/103).

Step A. (2*S*)-2-*tert*-Butoxycarbonylamino-3-(2-nitrophenyl-amino)-propionic acid. (2*S*)-2-*tert*-Butoxycarbonylamino-3-aminopropionic acid (10 g, 49 mmol), 2-fluoronitrobenzene (5.7 ml, 54 mmol), and NaHCO₃ (8.25 g, 98 mmol) was taken into 130 ml of DMF

- 479 -

and heated at 80 °C for 18 h. The reaction was evaporated *in vacuo* to give a viscous orange residue that was dissolved in 300 ml of H₂O and extracted with Et₂O (3 x 150 ml). The aq. solution was acidified to
5 pH 5 with 10% NaHSO₄ and extracted with EtOAc (3 x 250 ml). The combined extracts were dried over anhydrous Na₂SO₄, filtered, and evaporated to give 12.64 g (83%) of the title compound as an orange amorphous solid: ¹H
10 NMR (CD₃OD) δ 8.15-8.10 (1H, d), 7.54-7.48 (1H, t), 7.13-7.08 (1H, d), 6.73-6.65 (1H, t), 4.45-4.35 (1H, m), 3.9-3.8 (1H, dd), 3.65-3.55 (1H, dd), 1.45 (9H, s).

Step B. (2S)-2-tert-Butoxycarbonylamino-3-(2-aminophenyl-amino)-propionic acid. A mixture of (2S)-2-tert-Butoxycarbonylamino-3-(2-
15 nitrophenylamino)propionic acid (12.65 g, 40.5 mmol) and 0.5 g of 10% Pd/C in 100 ml of MeOH under hydrogen at 1 atmosphere was stirred for 4 h. The solution was filtered through Celite 545 and the filtrate evaporated *in vacuo* to afford the 11.95 g of the title compound in
20 quantitative yield as a dark brown solid that was used without purification: ¹H NMR (CD₃OD) δ 6.75-6.70 (3H, m), 6.65-6.58 (1H, m), 4.35-4.3 1H, m), 3.6-3.38 (2H, m), 1.45 (9H, s).

Step C. (3S)-2-Oxo-3-tert-Butoxycarbonylamino-1,3,4,5-tetrahydro-1H-1,5-benzodiazepine. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
25 (8.54 g, 44.5 mmol) was added to a cooled (0 °C) solution of (2S)-2-tert-butoxycarbonylamino-3-(2-aminophenylamino)propionic acid (11.95 g, 40.5 mmol) in
30 100 ml of DMF and stirred for 18 h. The reaction was poured into 700 ml of EtOAc and washed four times with

- 480 -

100 ml of H₂O. The organic layer was dried over anhydrous Na₂SO₄, filtered, and evaporated to give a brown solid that was purified by flash chromatography eluting with 3:7 EtOAc/hexane to give 8 g (71%) of the
5 title compound: ¹H NMR (CDCl₃) δ 7.78 (1H, s), 7.02-6.95 (1H, m), 6.88-6.82 (1H, m), 6.82-6.78 (1H, m), 6.75-6.70 (1H, m), 5.8-5.7 (1H, d), 4.55-4.45 (1H, m), 3.95 (1H, s), 3.9-3.82 (1H, m), 3.48-3.40 (1H, m), 1.45 (9H, s).

10 **Step D. (3S)-2-Oxo-3-tert-butoxycarbonylamino-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (600a/103).** A 1.0 M solution of lithium bis(trimethylsilyl)amide (3.4 ml, 3.4 mmol) in THF was added dropwise to a -78 °C solution of (3S)-2-oxo-3-
15 tert-butoxycarbonylamino-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine (0.94 g, 3.38 mmol) in 20 ml of anhydrous THF and stirred for 30 min. Methyl bromoacetate (0.44 ml, 4 mmol) was added dropwise to the reaction mixture then warmed to RT. The reaction
20 was diluted with 100 ml of EtOAc and washed with 0.3N KHSO₄ (50 ml), H₂O (2 x 50 ml), and brine. The combined organics were dried over anhydrous Na₂SO₄, filtered, and evaporated to afford a gum that was purified by flash chromatography eluting with 3:7
25 EtOAc/Hex. to give 0.98 g (83%) of the title compound as a white solid. ¹H NMR (CDCl₃) δ 7.15-7.07 (2H, m), 6.98-6.94 (1H, m), 6.88-6.84 (1H, d), 5.62-5.55 (1H, d), 4.71-4.65 (1H, d), 4.65-4.6 (1H, m), 4.33-4.27 (1H, d), 3.96-3.90 (1H, m), 3.78 (3H, s), 3.44-3.37 (1H, m),
30 1.4 (9H, s).

- 481 -

(3S)-2-Oxo-3-*tert*-butoxycarbonylamino-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (600b). Prepared by a similar method described for the preparation of 600a/103 (Step D), except benzyl bromoacetate was used instead of methyl bromoacetate to give 600b in quantitative yield.

(3S)-2-Oxo-3-*tert*-butoxycarbonylamino-2,3,4,5-tetrahydro-7,9-dimethyl-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (600c).

Sub
A15
10 Step A. (2S)-2-*tert*-Butoxycarbonylamino-3-(2-nitro-3,5-dimethylphenylamino)-propionic acid. Prepared by a method similar as described for 600a/103 (Step A), except 2-fluoro-4,6-dimethyl-nitrobenzene was used instead of 2-fluoronitrobenzene to give the desired
15 compound in 93% yield.

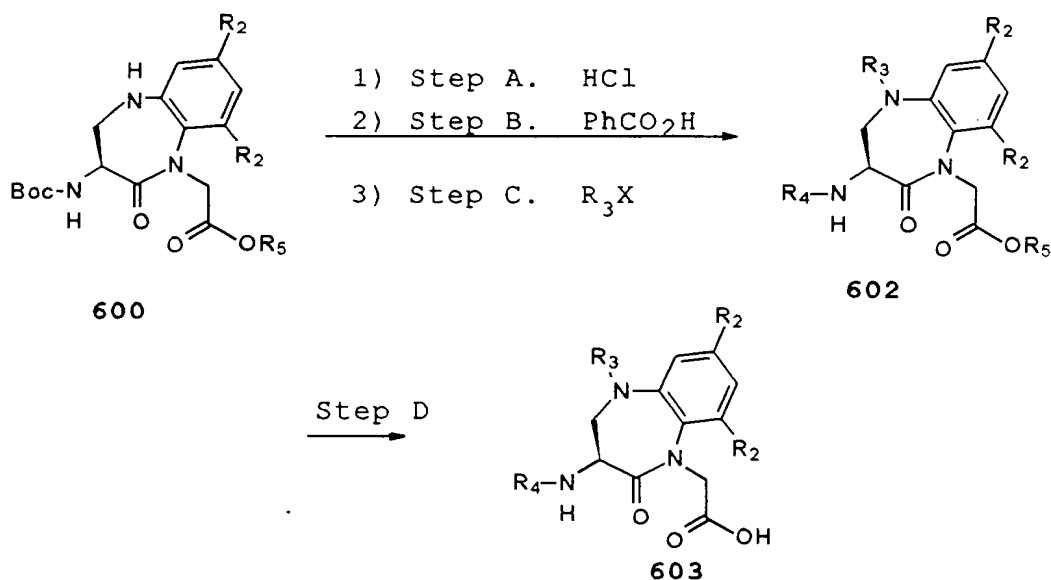
Sub
A16
20 Step B. (2S)-2-*tert*-Butoxycarbonylamino-3-(2-amino-3,5-dimethylphenyl-amino)-propionic acid. (2S)-2-*tert*-Butoxycarbonylamino-3-(2-nitro-3,5-dimethylphenyl-amino)propionic acid was converted to the title
20 compound in quantitative yield as described in the preparation of 600a/103 (Step B).

Step C. 2-Oxo-(3S)-3-*tert*-butoxycarbonylamino-2,3,4,5-tetrahydro-7,9-dimethyl-1H-1,5-benzodiazepine. A 0 °C solution of (2S)-2-*tert*-butoxycarbonylamino-3-(2-amino-3,5-dimethylphenyl-amino)-propionic acid (763 mg, 2.36
25 mmol) and N-methylmorpholine (483 mg, 4.78 mmol) in 60 ml of anhydrous THF was treated dropwise with isobutylchloroformate (352 mg, 2.5 mmol). The reaction was stirred for 2 h at 0 °C, at RT for 1h and poured
30 over EtOAc. The mixture was washed with aq. 5% NaHSO₄,

- 482 -

sat. aq. NaHCO_3 , and sat. aq. NaCl , dried over NaSO_4 , and concentrated *in vacuo*. Chromatography (flash, SiO_2 , 10% to 25% to 50 % $\text{EtOAc}/\text{CH}_2\text{Cl}_2$) gave 490 mg (68%) of the desired product.

- 5 **Step D.** (3*S*)-2-Oxo-3-*tert*-butoxycarbonylamino-2,3,4,5-tetrahydro-7,9-dimethyl-1*H*-1,5-benzodiazepine-1-acetic acid benzyl ester (600c). (2*S*)-2-*tert*-Butoxycarbonylamino-3-(2-amino-3,5-dimethylphenyl-amino)-propionic acid was converted to 600c, 75% by a
10 similar method for the preparation of 600b.



(3*S*)-2-Oxo-3-benzoylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid methyl ester (602a).

- Step A.** Anhydrous HCl was bubbled into a solution of
15 (3*S*)-2-oxo-3-*tert*-butoxycarbonylamino-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid methyl ester (600a/103, 4.0 g, 11.4 mmol) in 20 ml of CH_2Cl_2 for 20 min then stirred for 1 h at RT. The reaction

- 483 -

was evaporated to give (3*S*)-2-oxo-3-amino-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid methyl ester hydrochloride as a white solid.

Step B. The white solid was dissolved in 70 ml of DMF
5 and benzoic acid (1.5 g, 12.3 mmol) was added. The reaction was cooled in a ice/H₂O bath and treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.4 g, 12.5 mmol), 1-hydroxybenzotriazole (1.7 g, 12.6 mmol) and
10 diisopropylethylamine (3.0g, 23.2 mmol). The reaction was stirred for 18 h at RT under nitrogen atmosphere and poured onto H₂O. The aq. mixture was extracted with EtOAc (2x). The combined organic layers were washed with aq. 0.5 N NaHSO₄, H₂O, sat. aq. NaHCO₃, H₂O
15 and sat. aq. NaCl, dried over MgSO₄ and concentrated *in vacuo*. Chromatography (flash, SiO₂, 10% to 30% EtOAc/CH₂Cl₂) gave 3.4 g (85%) of (3*S*)-2-oxo-3-(benzoylamino)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid methyl ester as a white
20 solid.

Step C. Method A. (3*S*)-2-Oxo-3-benzoylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid methyl ester (602a). A solution of (3*S*)-2-oxo-3-(benzoylamino)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid methyl
25 ester (200 mg, 0.57 mmol) in CH₂Cl₂ (10 ml) was treated with triethylamine (119 mg, 1.13 mmol) and 3-phenylpropionyl chloride (114 mg, 0.68 mmol). The reaction was stirred at RT for 30 min and diluted with
30 CH₂Cl₂. The solution was washed with aq. 10% HCl, sat. aq. NaHCO₃ and sat. aq. NaCl, dried over Na₂SO₄ and

- 484 -

concentrated *in vacuo* to give 240 mg (87%) of 602a as a white foam.

Step C. Method B. (3S)-2-Oxo-3-benzoylamino-5-acetoacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (602g). A 0 °C solution of (3S)-2-oxo-3-(benzoylamino)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (**600b**) (465 mg, 1.10 mmol) in CH₂Cl₂ (5 ml) was treated with acetoacetic acid in 1 ml of CH₂Cl₂ followed by slow addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (431 mg, 2.2 mmol) in 2 ml of CH₂Cl₂ under N₂ atmosphere. After 15 min the reaction was poured onto EtOAc, washed with aq. 5 % NaHSO₄, dried over Na₂SO₄ and concentrated *in vacuo*. Chromatography (flash, SiO₂, 0% to 10% to 25% MeOH/CH₂Cl₂) gave 580 mg of (3S)-2-oxo-3-(benzoylamino)-5-acetoacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester as a white solid.

Step C. Method C. (3S)-2-Oxo-3-benzoylamino-5-methoxycarbonyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (602j). A vigorously-stirred, 0 °C solution of (3S)-2-oxo-3-(benzoylamino)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (**600b**) (461 mg, 1.07 mmol) in THF (5 ml) and sat. aq. NaHCO₃ (2.5 ml) was treated with a THF solution (0.35 ml) of methyl chloroformate (151 mg, 1.6 mmol) and the reaction was stirred for 45 min at RT. The reaction was poured onto CH₂Cl₂ and washed with H₂O, dried over Na₂SO₄ and concentrated *in vacuo*. Chromatography

- 485 -

(flash, SiO₂, 0% to 10% MeOH/CH₂Cl₂) gave 525 mg of 602j as a white solid.

- Step C. Method D. (3S)-2-Oxo-3-benzoylamino-5-benzylaminocarbonyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (602p).** A solution of 600a/103 (400 mg, 1.1mmol) and benzyliisocyanate (166 mg, 1.2mmol) in 10 ml of CH₂Cl₂ and 10 ml of DMF and heated at 80 °C for 3 days. The reaction was cooled to RT poured onto H₂O and extracted with EtOAc (2x). The combined organic layers were washed with H₂O (4x) and sat. aq. NaCl, dried over MgSO₄ and concentrated *in vacuo*. Chromatography (flash, SiO₂, 50% to 80% EtOAc/hexane) gave 440 mg (80%) of 602p as a white solid.
- Step C. Method E. (3S) 2-Oxo-3-benzylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (602v).** A solution of (3S) 2-oxo-3-amino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester hydrochloride (560 mg, 1.34 mmol), benzaldehyde (146 mg, 1.34 mmol) and sodium acetate (220 mg, 2.68 mmol) in methanol (20 ml) was treated with 4Å sieves (2 g) and NaCNBH₃ (168 mg, 2.68 mmol). The reaction was stirred for 2.5 h, acidified with 10% aq. HCl to pH 2 and washed with Et₂O (2x75 ml). The organic layers were concentrated *in vacuo* to give an oil. Chromatography (flash, SiO₂, 0 to 35% EtOAc/CH₂Cl₂) gave 250 mg (40%) of 602v as a clear oil.

- Step D. Method A. (3S)-2-Oxo-3-benzoylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-**

- 486 -

benzodiazepine-1-acetic acid (603a). (3S)-2-Oxo-3-benzoylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (602a; 1.25 g, 2.57 mmol) was dissolved in 11 ml of THF, MeOH and H₂O (5:5:1) and treated with LiOH·H₂O (42 mg, 0.62 mmol) stirred at RT for 64 h. The reaction was concentrated *in vacuo*, diluted with H₂O and acidified with aq. 1N HCl to give 230 mg of 603a as a white solid.

10 **Step D. Method B.** (3S) 2-Oxo-3-benzoylamino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid (603d). A mixture of (3S)-2-oxo-3-(benzoylamino)-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (602d; 510 mg, 1.08 mmol) and 15 5% Pd/C (250 mg) in MeOH (10 ml) stirred under H₂ (1 atm) for 0.5h. The reaction was filtered and concentrated *in vacuo* 410 mg of 603d as a white solid.

The compounds of Table 8 were prepared as described in Table 9, using the methods of Example 12.

20 **Table 8**

Compound no.	R ₂	R ₃	R ₄	R ₅
602b	H	PhCH ₂ C(O)	PhC(O)	CH ₂ Ph
602c	H	PhC(O)	PhC(O)	CH ₂ Ph
25 602d	H	CH ₃ C(O)	PhC(O)	CH ₂ Ph
602e	H	CH ₃ OCH ₂ C(O)	PhC(O)	CH ₂ Ph
602f	H	(CH ₃) ₂ CHCH ₂ C(O)	PhC(O)	CH ₂ Ph
602g	H	CH ₃ C(O)CH ₂ C(O)	PhC(O)	CH ₂ Ph

- 487 -

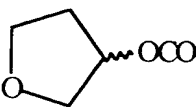
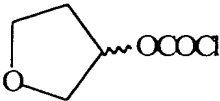
Compound no.	R ₂	R ₃	R ₄	R ₅
602h	H	CH ₃ OC(O)C(O)	PhC(O)	CH ₂ Ph
602i	H	CH ₃ C(O)C(O)	PhC(O)	CH ₂ Ph
602j	H	CH ₃ OC(O)	PhC(O)	CH ₂ Ph
602k	H	CH ₃ C(O)	Boc	CH ₂ Ph
5 602l	CH ₃	CH ₃ C(O)	Boc	CH ₂ Ph
602m	H	CH ₃ S(O ₂)	PhC(O)	CH ₃
602p	H	PhCH ₂ NHC(O)	PhC(O)	CH ₃
602q	H		PhC(O)	CH ₂ Ph
602r	H	PhCH ₂ CH ₂ C(O)	PhCH ₂ CH ₂ C(O)	CH ₂ Ph
10 602s	H	4-pyridylCH ₂ C(O)	PhC(O)	CH ₂ Ph

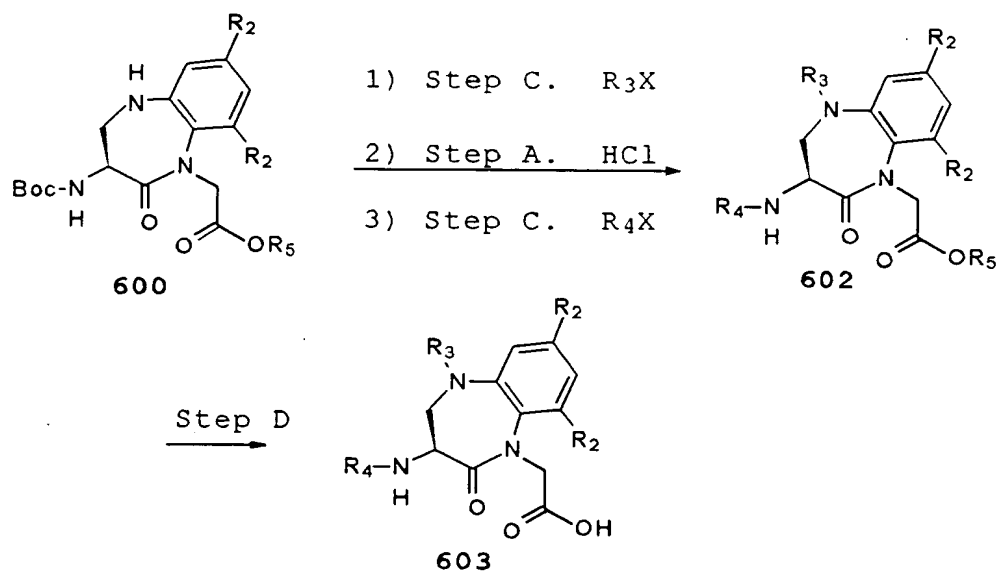
Table 9

No.	Starting material	R ₃ X	Step C method/ (% yield)	Step D method/ (% yield)
603b	600b	PhCH ₂ C(O)Cl	A (98)	B (89)
603c	600b	PhC(O)Cl	A (quant.)	B (quant.)
15 603d	600b	CH ₃ C(O)Cl	A (quant.)	B (quant.)
603e	600b	CH ₃ OCH ₂ C(O)Cl	A (59)	B (quant.)
603f	600b	(CH ₃) ₂ CHCH ₂ C(O)Cl	A (88)	B (95)
603g	600b	CH ₃ C(O)CH ₂ CO ₂ H	B (quant.)	B (quant.)
603h	600b	CH ₃ OC(O)C(O)Cl	A (96)	B (quant.)
20 603i	600b	CH ₃ C(O)CO ₂ H	B (87)	B (94)
603j	600b	CH ₃ OC(O)Cl	C (quant.)	B (quant.)

- 488 -

No.	Starting material	R ₃ X	Step C method/ (% yield)	Step D method/ (% yield)
603k	600b	CH ₃ C(O)Cl	A, Step C only (quant.)	not run
603l	600c	CH ₃ C(O)Cl	A, Step C only (quant.)	not run
603m	600a/103	CH ₃ SO ₃ Cl, NEt ₃ instead of pyridine and THF instead of CH ₂ Cl ₂	A (76)	A (92)
603p	600a/103	PhCH ₂ C=N=O	D (80)	A (86)
603q	600b		C (83)	B (71)
603r	600a/103	PhCH ₂ CH ₂ C(O)Cl	A	
603s	600b	4-pyridylCH ₂ CO ₂ H	B (90)	B (98)

5



The compounds of Table 10 were prepared as described in Table 11 using the methods of Example 12.

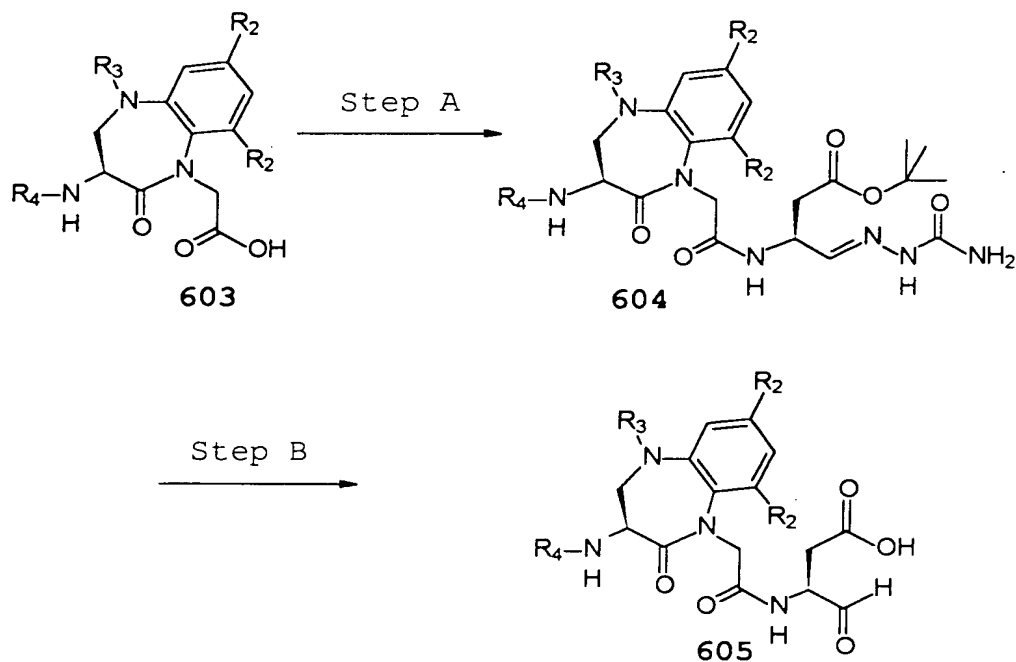
Table 10

Compound no.	R ₂	R ₃	R ₄	R ₅
602n	H	CH ₃ C(O)	Naphthylene-2-C(O)	CH ₂ Ph
602o	CH ₃	CH ₃ C(O)	PhC(O)	CH ₂ Ph
602t	H	3-CH ₃ PhCH ₂ C(O)	PhC(O)	CH ₂ Ph
602u	H	CH ₃ C(O)	Fmoc	CH ₂ Ph
602v	H	PhCH ₂ CH ₂ CO	PhCH ₂	CH ₃

Table 11

No.	Starting material	1) Step C. R ₃ X method (% yield)	3) Step C R ₄ X method (% yield)	Step D method (% yield)
603n	602k	CH ₃ C(O)Cl A (quant.)	naphthylene- 2-C(O)Cl A (70)	B (quant.)
603o	602l	CH ₃ C(O)Cl A (quant.)	PhC(O)Cl A (73)	B (quant.)
603t	602k	3- CH ₃ PhCH ₂ C(O)Cl A (quant.)	PhC(O)Cl A (93)	B (95)
603u	602k	CH ₃ C(O)Cl A (quant.)	Fmoc-Cl C (82)	C (98)
603v	600a/103	PhCH ₂ CH ₂ C(O)Cl A	PhCHO E (40)	A (95)

- 490 -

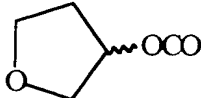


The compounds of Table 12 were prepared by the methods described below.

Table 12

compound no.	R_2	R_3	R_4
5 605a	H	PhCH ₂ CH ₂ C(O)	PhC(O)
605b	H	PhCH ₂ C(O)	PhC(O)
605c	H	PhC(O)	PhC(O)
605d	H	CH ₃ C(O)	PhC(O)
605e	H	CH ₃ OCH ₂ C(O)	PhC(O)
10 605f	H	(CH ₃) ₂ CHCH ₂ C(O)	PhC(O)
605g	H	CH ₃ C(O)CH ₂ C(O)	PhC(O)
605h	H	CH ₃ OC(O)C(O)	PhC(O)
605i	H	CH ₃ C(O)C(O)	PhC(O)
605j	H	CH ₃ OC(O)	PhC(O)

- 491 -

compound no.	R ₂	R ₃	R ₄
605m	H	CH ₃ SO ₃	PhC(O)
605n	H	CH ₃ C(O)	Naphthyl-2-C(O)
605o	CH ₃	CH ₃ C(O)	PhC(O)
605p	H	PhCH ₂ NHC(O)	PhC(O)
5 605q	H		PhC(O)
605s	H	4-pyridylCH ₂ C(O)	PhC(O)
605t	H	3-CH ₃ PhCH ₂ C(O)	PhC(O)
605v	H	PhCH ₂ CH ₂ C(O)	PhCH ₂

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605a).

Step A. (3S)-3-(1-Fluorenylmethyloxycarbonylamino)-4-oxobutyric acid tert-butyl ester semicarbazone (210 mg, 0.45 mol, Prepared in a similar manner to the benzyloxycarbonyl analog in Graybill et al., Int. J. Protein Res., 44, pp. 173-82 (1994).) was dissolved in 10 ml of DMF and 2 ml of diethylamine and stirred for 2 h. The reaction was concentrated *in vacuo* to give (3S)-3-amino-4-oxobutyric acid tert-butyl ester semicarbazone. The 0 °C solution of the above residue and **603a** (200 mg, 0.42mmol) in 5 ml of DMF and 5 ml of CH₂Cl₂ was treated with 1-hydroxybenzotriazole (57 mg, 0.42mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (98 mg, 0.51 mmol). The reaction was stirred at RT for 18 h, poured onto

- 492 -

EtOAc (75 ml) and washed with aq. 0.3 N KHSO₄, sat. aq. NaHCO₃ and sat. aq. NaCl, dried over NaSO₄ and concentrated *in vacuo*. Chromatography (flash, SiO₂, 0% to 4% MeOH/0.1% NH₄OH/CH₂Cl₂) to give 240 mg (83%) of
5 604a.

Step B. 604a was stirred with 10 ml of 33% TFA/H₂O for 4 h and concentrated *in vacuo*. The residue was dissolved in 7 ml of MeOH/acetic acid/37% aq. formaldehyde (5:1:1) and stirred for 18 h.
10 Chromatography (Reverse Phase C18, 4.4mm ID x 25 cm, 15% to 70% CH₃CN/0.1% TFA/H₂O) gave 32 mg (16%) of 605a as a white solid: ¹H NMR (CD₃OD, existing as diastereomers of the hemiacetal) δ 7.85-7.78 (2H, d), 7.5-7.32 (6H, m), 7.32-7.28 (1H, m), 7.18-6.98 (5H, m),
15 4.92-4.85 (2H, m), 4.5-4.32 (2H, m), 4.31-4.20 (2H, m), 3.7-3.6 (1H, m), 2.90-2.75 (2H, m), 2.65-2.5 (1H, m), 2.48-2.25 (3H, m).

The following compounds were prepared by a similar method:

20 (3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-phenylacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605b). 148 mg (33%) as a white solid: ¹H NMR(CD₃OD) δ 7.9-6.9 (m, 16H), 4.9 (s, 2H), 4.5 (m, 1H), 4.4 (m, 2H), 3.75 (s, 1H), 3.6
25 (dd, 1H), 3.45 (dd, 1H), 2.7 (m, 1H), 2.5 (m, 1H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-benzoyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605c). 319 mg (56%) as a white solid: ¹H NMR(CD₃OD) δ 7.9-6.9 (m, 16H), 5.1 (m, 1H), 4.9 (dd,

- 493 -

1H), 4.7 (m, 1H), 4.6 (dd, 1H), 4.4 (m, 2H), 4.05 (m, 1H), 2.7 (m, 1H), 2.5 (m, 1H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-
5 butyric acid (605d). 190 mg (38%) as a white solid:
¹H NMR(CD₃OD) δ 1.9(d, H), 2.4(m, 1H), 2.65(m, 1H), 3.7(m, 1H), 4.25(m, 1H), 4.45(m, 2H), 4.8-5.05(m, 3H), 7.3-7.7(m, 7H), 7.9(d, 2H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-methoxyacetyl-
10 2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605e). 250 mg (78%)
¹H NMR (CD₃OD) δ 1.87 (bs), 1.95 (s, 2H), 2.1 (bs), 2.4 (m, 2H), 2.65 (m, 2H), 3.59 (bs), 3.75 (bs), 3.87 (bs), 4.19 (m), 4.37 (m), 4.50-4.78 (bm), 4.92 (m), 5.27
15 (bs), 7.41-7.58 (m, 7H), and 7.87 ppm (d, 2H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(3-methylbutyryl)-
2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605f). 210.5 mg (46%)
as a white solid: ¹H NMR(CD₃OD) δ 7.9-7.4 (m, 9H), 5.1
20 (m, 1H), 4.9 (m, 1H), 4.6 (dd, 1H), 4.4 (m, 2H), 4.1 (d, 1H), 3.8 (m, 1H), 3.5 (q, 1H), 2.7 (m, 1H), 2.5 (m, 1H), 2.0 (m, 3H), 1.2 (t, 1H), 0.9 (d, 3H), 0.8 (d, 3H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-acetoacetyl-
25 2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605g). 81 mg (19%) as
a white solid: ¹H NMR(CD₃OD) δ 7.9-7.3 (m, 11H), 4.9-4.8 (m, 2H), 4.6-4.4 (m, 3H), 4.3 (m, 1H), 3.75 (q,

- 494 -

1H), 3.55 (d, 1H), 2.7 (m, 1H), 2.5 (m, 1H), 2.05 (s, 3H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-methyloxalyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605h). 227 mg (54%) of a white solid: ^1H NMR(CD₃OD) δ 2.5(m, 1H), 2.7(m, 1H), 3.55(s, 3H), 3.8-4.0(m, 2H), 4.4(m, 1H), 4.6-4.8(m, 2H), 4.95(d, 1H), 5.1(m, 1H), 7.3-7.7(m, 7H), 7.9(d, 2H), 8.6(d, 1H).

10 (3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-acetylcarbonyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605i). 150 mg (37%) as a white solid: ^1H NMR(CD₃OD) δ 7.9-7.3 (m, 12H), 5.1 (m, 1H), 4.65 (t, 1H), 4.55 (dd, 1H), 4.35 (m, 1H), 4.1 (d, 1H), 3.9 (q, 1H), 3.45 (q, 1H), 2.7 (m, 1H), 2.5 (m, 1H), 2.25 (s, 3H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-methoxycarbonyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605j). 234 mg (44%) as a white solid: ^1H NMR(CD₃OD) δ 7.9-7.4 (m, 12H), 5.0 (m, 1H), 4.8-4.5 (m, 3H), 4.4 (m, 1H), 4.3 (t, 1H), 3.9-3.75 (m, 2H), 3.6 (s, 3H), 2.7 (m, 1H), 2.5 (m, 1H).

506
A17
25 ~~(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-methanesulfonyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605m). 64.5 mg (34%) as a white solid: ^1H NMR (DMSO-d₆, existing as diastereomers of the hemiacetal & open form of the aldehyde) δ 9.48 (0.2H, s), 8.85-8.72 (1H, m), 8.65-~~

- 495 -

Sub
A17

8.60 (0.8 H, d), 8.30-8.26 (0.2 H, d), 7.95-7.88
(2H, d), 7.6-7.45 (6H, m), 7.44-7.38 (1H, m), 5.78-5.75
(0.2H, d), 5.48 (0.6H, s), 4.85-4.70 (2H, m), 4.62-4.54
(1H, d), 4.50-4.40 (2H, m), 4.25-4.14 (1H, m), 3.9-3.85
5 (1H, m), 3.16 (3H, s), 3.05-2.3 (2, m).

Sub
A18

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(naphthlene-2-
carbonyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-
acetylamino]4-oxo-butyric acid (605n). 103 mg (17%) as
a white solid: ^1H NMR (CD_3OD) δ 1.9(s, 3H), 2.5(m,
10 1H), 2.65(m, 1H), 3.75(m, 1H), 4.3(m, 1H), 4.5-4.7(m,
3H), 4.85-5.1(m, 2H), 7.3-7.65(m, 6H), 7.85-8.05(m,
4H), 8.45(s, 1H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-acetyl-2,3,4,5-
tetrahydro-7,9-dimethyl-1H-1,5-benzodiazepin-1-
15 acetylamino]4-oxo-butyric acid (605o). 42 mg (12%) as
a white solid: ^1H NMR (CD_3OD , existing as
diastereomers of the hemiacetal) δ 7.85-7.74 (2H, m),
7.5-7.44 (1H, m), 7.43-7.35 (4H, m), 5.6-5.05 (2H, m),
4.82-4.42 (2H, m), 4.40-3.95 (2H, m), 3.6-3.5 (1H, m),
20 2.7-2.38 (2H, m), 2.32 (3H, s), 2.27 (3H, s), 1.92
(3H, s).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-
benzylaminocarbonyl-2,3,4,5-tetrahydro-1H-1,5-benzo
diazepin-1-acetylamino]4-oxo-butyric acid (605p). 165
25 mg (37%) as a white solid: ^1H NMR (CD_3OD) δ 2.45(m,
1H), 2.7(m, 1H), 3.8(m, 1H), 4.15-4.5(m, 4H), 4.5-
4.75(m, 2H), 4.8-5.0(m, 2H), 7.1-7.7(m, 12H), 7.9(d,
2H).

- 496 -

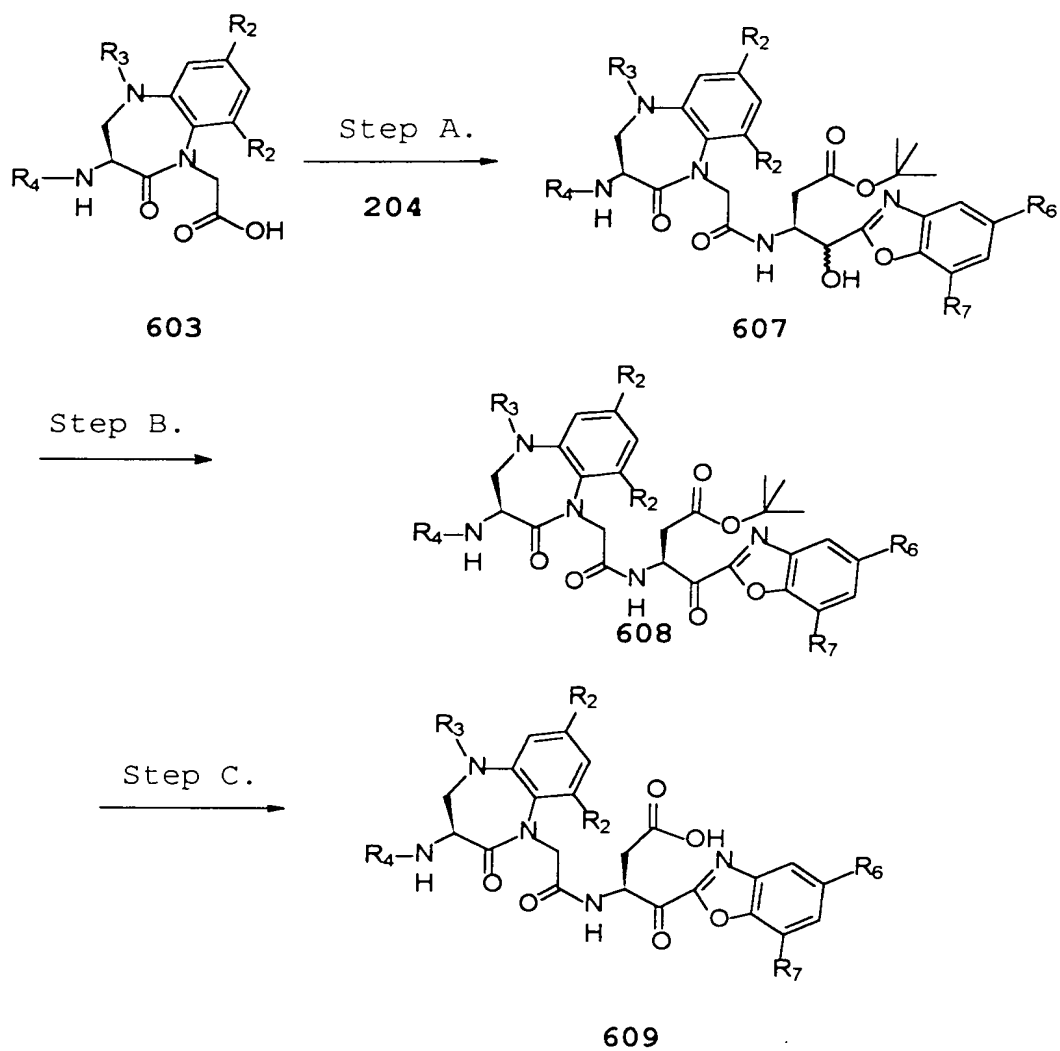
(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-[(3R,S) 3-tetrahydrofuranylmethoxycarbonyl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605q). 210 mg (66%) ¹H NMR (CD₃OD) δ 1.95 (s, 2H),
 5 2.4 (m, 2H), 2.65 (m, 2H), 3.29 (s, 3H), 3.78 (m), 3.87 (bs), 4.0 (d, 1H), 4.32 (m), 4.50-4.15 (m), 4.95 (m), 5.27 (bs), 7.45-7.65 (m, 7H), and 7.89 ppm (d, 2H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(4-pyridylacetyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605s). 128 mg (19%) as
 10 a white solid: ¹H NMR(CD₃OD) δ 8.5-7.4 (m, 13H), 5.0 (m, 1H), 4.7 (m, 1H), 4.5 (m, 2H), 4.45-4.4 (m, 3H), 3.8-3.7 (m, 2H), 2.7 (m, 1H), 2.5 (m, 1H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(3-methylphenylacetyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605t).
 15 132 mg (24%) as a white solid: ¹H NMR(CD₃OD) δ 7.8-6.7 (m, 13H), 4.9 (t, 1H), 4.75 (dd, 1H), 4.2 (dd, 1H), 4.1 (m, 2H), 3.8 (dd, 1H), 3.6 (q, 1H), 3.45 (dd, 1H), 3.3
 20 (dd, 1H), 2.6 (m, 1H), 2.3 (m, 1H), 2.15 (s, 3H).

(3S) 3-[(3S) 2-Oxo-3-benzylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid trifluoroacetic acid salt (605v). 88 mg (28%) as a white solid: ¹H NMR
 25 (CD₃OD) δ 7.63-7.51 (2H, m), 7.5-7.35 (7H, m), 7.25-7.10 (3H, m), 7.1-7.02 (2H, m), 5.04-4.96 (1H, m), 4.75-4.57 (2H, m), 4.38-4.26 (2H, m), 4.24-4.12 (2H, m), 4.10-4.02 (1H, d), 4.88-4.80 (1H, m), 2.90-2.80 (2H, m), 2.78-2.63 (1H, m), 2.55-2.35 (2H, m), 2.34-2.22 (1H, m).

- 497 -



The compounds of Table 13 are described below.

Table 13

#	R ₂	R ₃	R ₄	R ₆	R ₇
609a	H	PhCH ₂ CH ₂ C (O)	PhCH ₂ CH ₂ C (O)	Cl	Cl
609b	H	CH ₃ C (O)	PhC (O)	Cl	Cl

- 498 -

(3S)-3-[(3S)-2-Oxo-3-(3-phenylpropionylamino)-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]-4-(5,7-dichlorobenzoxazol-2-yl)-4-oxo-butyric acid (609a).

Sub
A19

5 **Step A.** A solution of **204** (223 mg, 0.5 mmol) and **603r** (300mg; 0.36 mmol) in 4 ml of DMF and 4 ml of CH₂Cl₂ was treated with (Ph₃P)₂PdCl₂ (10 mg), 1-hydroxybenzotriazole (135 mg, 1.0 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (115 mg, 0.6 mmol). Tri-n-butyl tin hydride (219 mg, 0.75 mmol) was added dropwise to the reaction and stirred for 18 h. The reaction was poured onto EtOAc and washed with aq. 10% NaHSO₄, sat. aq. NaHCO₃ and sat. aq. NaCl, dried over Na₂SO₄ and concentrated in vacuo. Chromatography (flash, SiO₂, 0% to 50% EtOAc/hexane) gave 360 mg (86%) of **607a** as a foam.

20 **Step B.** A solution of **607a** (360 mg) in 5 ml of CH₂Cl₂ was added dropwise to a suspension of 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodioxol-3(1H)-one (362 mg, 0.85 mmol) in 20 ml of CH₂Cl₂. The reaction was stirred for 4.5 h, diluted with CH₂Cl₂ and washed with a 1:1 mixture of sat. aq. NaHCO₃/sat. aq. Na₂S₂O₃, sat. aq. NaHCO₃ (2x) and sat. aq. NaCl, dried over Na₂SO₄ and concentrated in vacuo. Chromatography (flash, SiO₂, 20% EtOAc/CH₂Cl₂) gave 340 mg (95%) of the ketone **608a**.

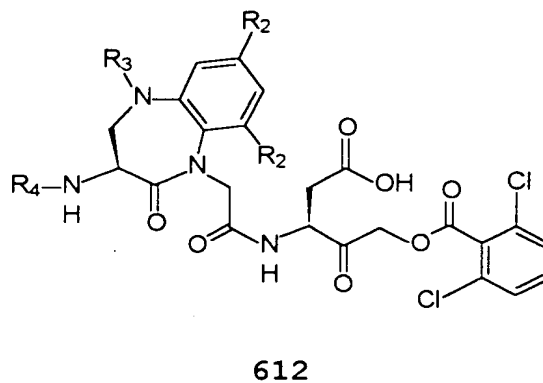
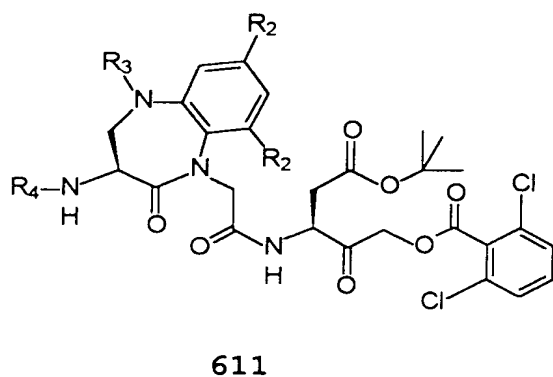
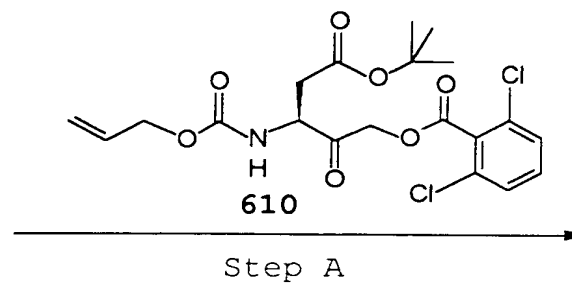
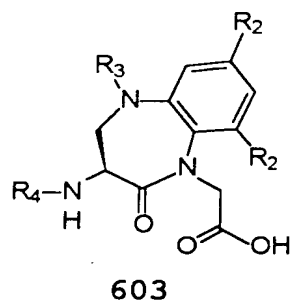
30 **Step C.** **608a** (300 mg, 0.36 mmol) was dissolved in 25 ml of 25% TFA/CH₂Cl₂ and stirred at RT for 5 h and concentrated in vacuo. Chromatography (flash, SiO₂, 0 to 5% MeOH/CH₂Cl₂) gave 118 mg (42%) of **609a** as a white solid: ¹H NMR (CD₃OD) δ 7.62-6.65 (16H, m), 4.85-4.7

- 499 -

(1H, m), 4.68-4.42 (2H, m), 4.40-4.15 (2H, m), 3.48-3.28 (1H, m), 3.0-2.9 (1H, m), 2.9-2.6 (4H, m), 2.55-2.18 (3H, m), 2.16-1.96 (2H, m).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]-4-(5,7-dichlorobenzoxazol-2-yl)-4-oxo-butyric acid (609b) was prepared from 603d in a similar manner as 609a to give 287 mg (43% overall yield) as white solid: ¹H NMR(DMSO-d₆) δ 1.6(s, 3H), 2.7-3.1(m, 2H), 3.45(m, 1H), 4.4(t, 1H), 4.7(m, 2H), 4.95(m, 1H), 5.2, 5.4(2s, 1H), 7.2-7.65(m, 8H), 7.9(d, 2H), 8.8(t, 1H), 8.9,9.1(2s, 1H), 12.6(br, 1H).

- 500 -



(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-methanesulfonyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl-amino]-5-(2,6-dichlorobenzoyloxy)-4-oxo-pentanoic acid (612) was prepared by a method similar as 607a

5 (Steps A and C only) using 603m (150 mg, 0.36 mmol)

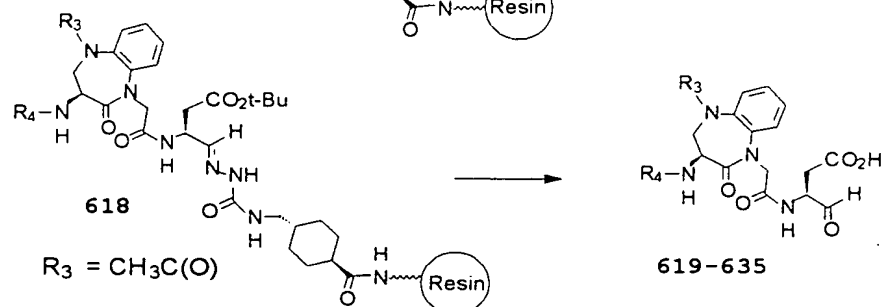
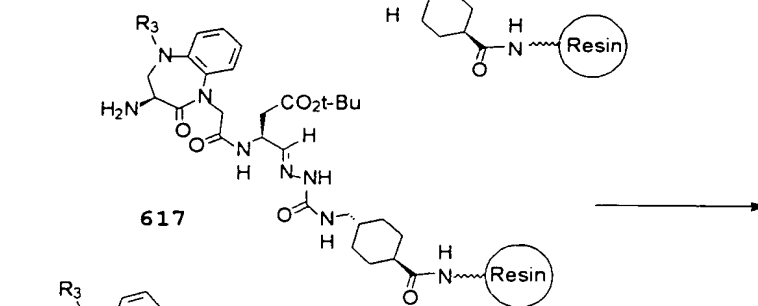
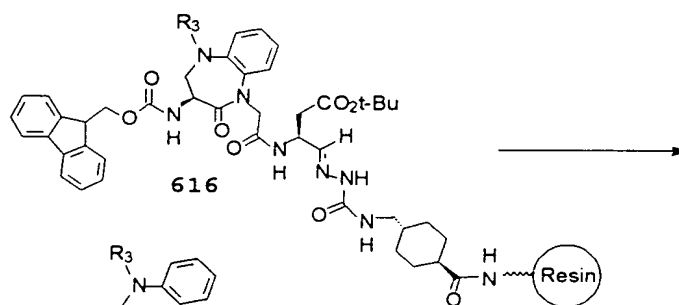
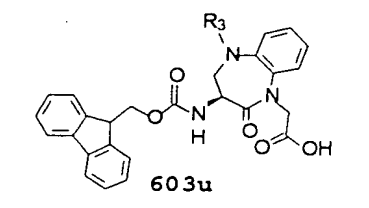
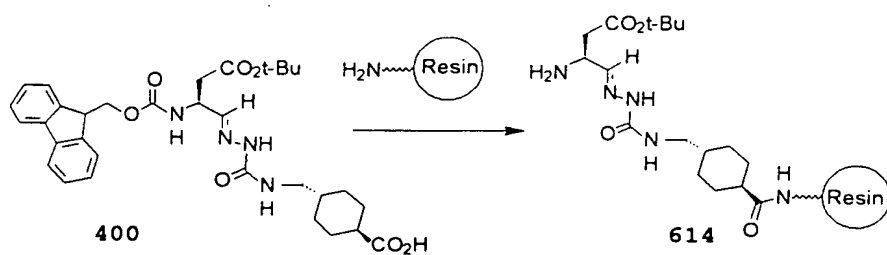
- 501 -

instead of **603r** and (3*S*)-3-(allyloxycarbonylamino)-4-oxo-5-(2,6-dichlorobenzoyl-oxy)pentanoic acid *t*-butyl ester (110; 160 mg, 0.36 mmol, WO 93/16710) instead of **606a** to give **612** (56%) as a white solid: ¹H NMR
5 (CDCl₃) 7.85-7.10 (12H, m), 5.4-4.65 (4H, m), 4.6-4.15 (4H, m), 3.10-2.72 (5H, s & m).

Example 13

Compounds **619-635** were synthesized as described in Example 13 and Table 14.

- 502 -



- 503 -

Syntheses of 619-635.

Step A. Synthesis of 614. TentaGel S® NH₂ resin (0.16 mmol/g, 10.0 g) was placed in a sintered glass funnel and washed with dimethylformamide (3 X 50 mL), 5 10% (v/v) diisopropylethylamine (DIEA) in dimethylformamide (2 X 50 mL) and finally with dimethylformamide (4 X 50 mL). Sufficient dimethylformamide was added to the resin to obtain a slurry followed by 400 (1.42 g, 2.4 mmol, prepared from 10 (3S) 3-(fluorenylmethoxycarbonyl)-4-oxobutryic acid t-butyl ester according to A.M. Murphy et. al. J. Am. Chem. Soc., 114, 3156-3157 (1992)), 1-hydroxybenzotriazole hydrate (HOBT·H₂O; 0.367 g, 2.4 mmol), O-benzotriazole-N,N,N',N'-tetramethyluronium 15 hexafluorophosphate (HBTU; 0.91 g, 2.4 mmol), and DIEA (0.55 mL, 3.2 mmol). The reaction mixture was agitated overnight at room temperature using a wrist arm shaker. The resin was isolated on a sintered glass funnel by suction filtration and washed with dimethylformamide (3 20 X 50 mL). Unreacted amine groups were then capped by reacting the resin with 20% (v/v) acetic anhydride/dimethylformamide (2 X 25 mL) directly in the funnel (10 min/wash). The resin was washed with dimethylformamide (3 X 50 mL) and dichloromethane (3 X 25 50 mL) prior to drying overnight *in vacuo* to yield **614** (11.0 g, quantitative yield).

Step B. Synthesis of 616. Resin **614** (3.0 g, 0.16 mmol/g, 0.48 mmol) was swelled in a sintered glass funnel by washing with dimethylformamide (3 X 15 mL). 30 The Fmoc protecting group was then cleaved with 25% (v/v) piperidine/dimethylformamide (15 mL) for 10 min

- 504 -

(intermittent stirring) and then for 20 min with fresh piperidine reagent (15 ml). The resin was then washed with dimethylformamide (3 X 15 ml), followed by N-methypyrrolidone (2 X 15 mL). After transferring the resin to a 100 mL flask, N-methypyrrolidone was added to obtain a slurry followed by **603u** (0.736 g, 0.72 mmol), HOBT·H₂O (0.112 g, 0.73 mmol), HBTU (0.27 g, 0.73 mmol) and DIEA (0.26 mL, 1.5 mmol). The reaction mixture was agitated overnight at room temperature using a wrist arm shaker. The resin work-up and capping with 20% (v/v) acetic anhydride in dimethylformamide were performed as described for **614** to yield **616** (3.13 g, quantitative yield).

Step C. Synthesis of 617. This compound was prepared from resin **616** (0.24 g, 0.038 mmol) using an Advanced ChemTech 396 Multiple Peptide synthesizer. The automated cycles consisted of a resin wash with dimethylformamide (3 X 1 mL), deprotection with 25% (v/v) piperidine in dimethylformamide (1 mL) for 3 min followed by fresh reagent (1 mL) for 10 min to yield resin **617**. The resin was washed with dimethylformamide (3 X 1 mL) and N-methypyrrolidone (3 X 1 mL).

Step D. Method 1. (624). Resin **617** was acylated with a solution of 0.4M thiophene-3-carboxylic acid and 0.4M HOBT in N-methypyrrolidone (1 mL), a solution of 0.4M HBTU in N-methypyrrolidone (0.5 mL) and a solution of 1.6M DIEA in N-methypyrrolidone (0.35 mL) and the reaction was shaken for 2 hr at room temperature. The acylation step was repeated. Finally, the resin was washed with dimethylformamide (3 X 1 mL), dichloromethane (3 X 1 mL) and dried *in vacuo*.

- 505 -

The aldehyde was cleaved from the resin and globally deprotected by treatment with 95% TFA/ 5% H₂O (v/v, 1.5 mL) for 30 min at room temperature. After washing the resin with cleavage reagent (1 mL), the combined
5 filtrates were added to cold 1:1 ether:pentane (12 mL) and the resulting precipitate was isolated by centrifugation and decantation. The resulting pellet was dissolved in 10% acetonitrile/90% H₂O/0.1% TFA (15 mL) and lyophilized to obtain crude **624** as a white
10 powder. The compound was purified by semi-prep RP-HPLC with a Rainin Microsorb™ C18 column (5 u, 21.4 X 250 mm) eluting with a linear acetonitrile gradient (5% - 45%) containing 0.1% TFA (v/v) over 45 min at 12 mL/min. Fractions containing the desired product were
15 pooled and lyophilized to provide **624** (10.0 mg, 54%).

Step D. Method 1A. Synthesis of 627. Following a similar procedure as method 1, resin **617** was acylated with 4-(1-fluorenylmethoxycarbonylamino)benzoic acid and repeated. The Fmoc group was removed as described
20 in Step C and the free amine was acetylated with 20% (v/v) acetic anhydride in dimethylformamide (1 mL) and 1.6M DIEA in N-methylpyrrolidone (0.35 mL) for 2 hr at room temperature. The acetylation step was repeated. Cleavage of the aldehyde from the resin gave **627** (4.2
25 mg, 20%).

Step D. Method 2. Synthesis of 632. Following a similar procedure as method 1, resin **617** was acylated with 0.5M cinnamoyl chloride in N-methylpyrrolidone (1 mL) and 1.6M DIEA in N-methylpyrrolidone (0.35 mL) for 2
30 hr at room temperature. The acylation step was

- 506 -

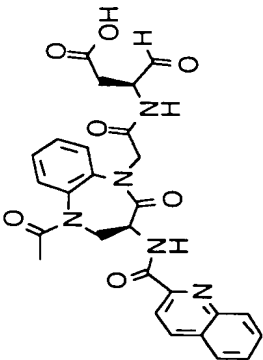
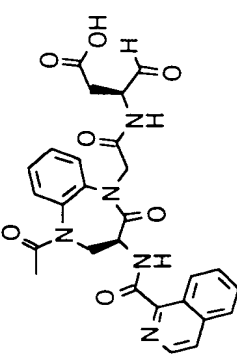
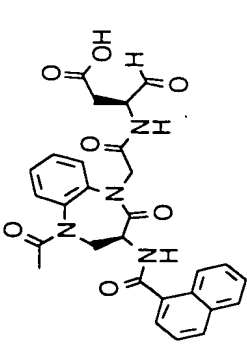
repeated. Cleavage of the aldehyde from the resin gave **632** (11.1 mg, 58%).

Step D. Method 3. Synthesis of 629. Following a similar procedure as method 1, resin **617** was reacted
5 with 1.0M benzenesulfonyl chloride in dichloromethane (0.5 mL) and 1M pyridine in dichloromethane (0.60 mL) for 4 hr at room temperature. The reaction was repeated. Cleavage of the aldehyde from the resin **629** (4.7 mg, 24%).

10 **Analytical HPLC methods:**

(1) Waters DeltaPak C18, 300A (5u, 3.9 X 150 mm).
Linear acetonitrile gradient (5% - 45%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.

Table 14

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) ⁺	Syn. Method
619		C ₂₇ H ₂₅ N ₅ O ₇	531.53	11.71 (1) 98%	532	1
620		C ₂₇ H ₂₅ N ₅ O ₇	531.53	10.44 (1) 98%	532	1
621		C ₂₈ H ₂₆ N ₄ O ₇	530.54	11.57 (1) 98%	(M+Na) ⁺ 553	2

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) ⁺	Syn. Method
622		C28H26N4O8	546.54	10.19 (1) 98%	(M+Na) ⁺ 569	1
623		C39H32N4O10	716.71	15.8 (1) 09%	(M-) 716	1
624		C22H22N4O7S	486.51	8.39 (1) 98%	487	1

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) ⁺	Syn. Method
625		C23H25N5O7S	515.55	7.60 (1) 98%	516	1
626		C25H26N4O8	510.51	7.58 (1) 98%	511	1
627		C26H27N5O8	537.53	7.96 (1) 98%	538	1A

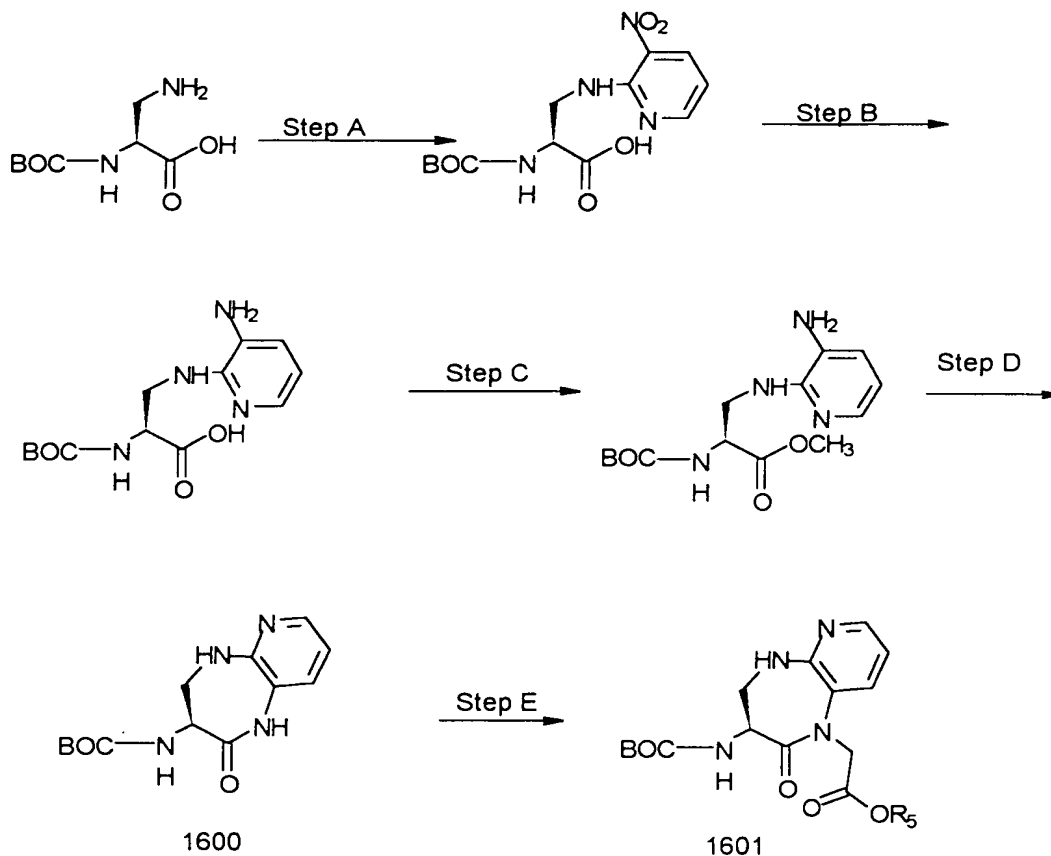
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) ⁺	Syn. Method
628		C25H24N4O9	524.49	9.50 (1) 98%	525	1
629		C23H24N4O8S	516.53	9.85 (1) 98%	517	3
630		C25H26N4O7	494.51	9.25 (1) 98%	495	2
631		C24H26N4O8S	530.56	10.19 (1) 98%	531	3

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) ⁺	Syn. Method
632		C26H26N4O7	506.52	10.99 (1) 98%	507	2
633		C25H26N4O8	510.51	11.48 (1) 98%	511	2
634		C22H26N4O9	490.47	6.87 (1) 98%	491	2
635		C25H24N4O8	508.49	10.03 (1) 98%	509	1

- 512 -

Example 14

Compounds 1605a-j, 1605m, 1605n, 1605p, 1605t, and 1605v were synthesized as described below.



(3S) N-(2-Oxo-3-tert-butoxycarbonylamino-2,3,4,5-tetrahydro-1H-pyrido [3,4-b][1,4-diazepine (1600)).

Step A. (2S) 2-tert-Butoxycarbonylamino-3-(3-nitropyridin-2-ylamino)propionic acid was prepared by a similar method as (2S) 2-tert-butoxycarbonylamino-3-(2-nitrophenyl-amino)propionic acid in Step A of the synthesis of 600a/103, except that 3-chloro-3-nitro pyridine was used instead of 2-

- 513 -

fluoronitrobenzene, to give 4.05 g (64%) of a yellow solid.

Step B. (2S) 2-tert-Butoxycarbonylamino-3-(3-aminopyridin-2-ylamino)propionic acid was prepared by a similar method to (2S) 2-tert-Butoxycarbonylamino-3-(2-aminophenylamino)-propionic acid in Step B of the synthesis of 600a/103 to give 3.68 g (quant.) as a dark solid.

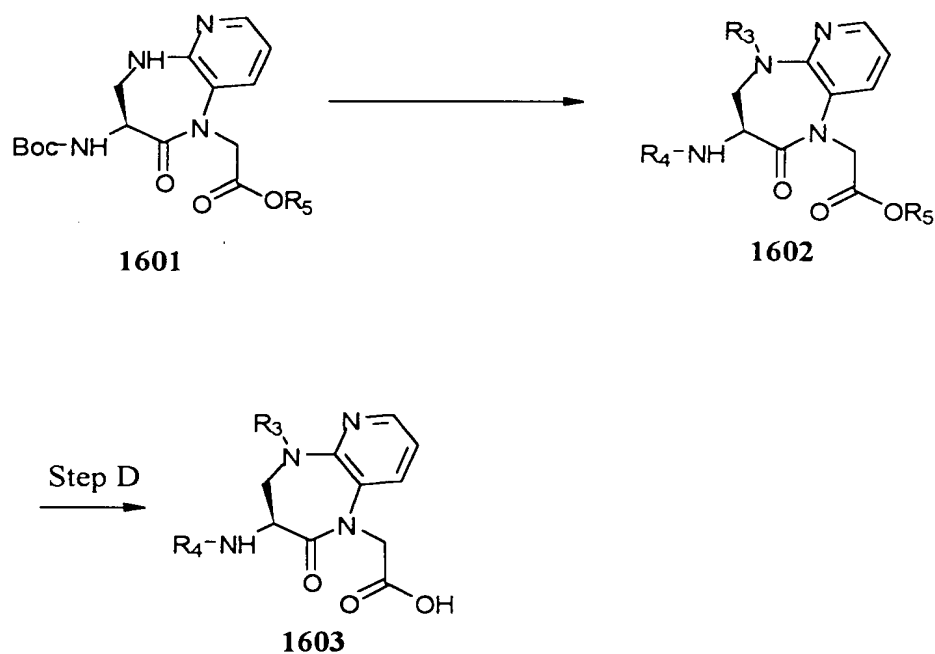
Step C. (2S) 2-tert-Butoxycarbonylamino-3-(3-aminopyridin-2-ylamino)propionic acid methyl ester. A solution of (2S) 2-tert-Butoxycarbonylamino-3-(3-aminopyridin-2-ylamino)-propionic acid (360 mg, 1.21 mmol) and MeOH (59 mg, 1.82 mmol) in anhydrous CH₂Cl₂ (20 ml) was treated with 4-dimethylaminopyridine (DMAP, 163 mg, 1.33 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (280 mg, 1.45 mmol). The reaction was stirred for 18 h, diluted with EtOAc (150ml), washed with water (2x), sat. aq. NaHCO₃, and sat. aq. NaCl, dried over Na₂SO₄ and concentrated *in vacuo*. Chromatography (flash, SiO₂, 0 to 5% MeOH/CH₂Cl₂) gave 250 mg (67%) of the title compound as a light tan solid.

Step D. (3S) N-(2-Oxo-3-tert-butoxycarbonylamino-2,3,4,5-tetrahydro-1H-pyrido[3,4-b][1,4-diazepine (1600)). A solution of (2S) 2-tert-butoxycarbonylamino-3-(3-aminopyridin-2-ylamino)propionic acid methyl ester (70 mg, 0.225 mol) and 25% sodium methoxide/MeOH (130 μ l, 0.56 mmol) in anhydrous MeOH (4 ml) was heated at 60°C for 16 h.

- 514 -

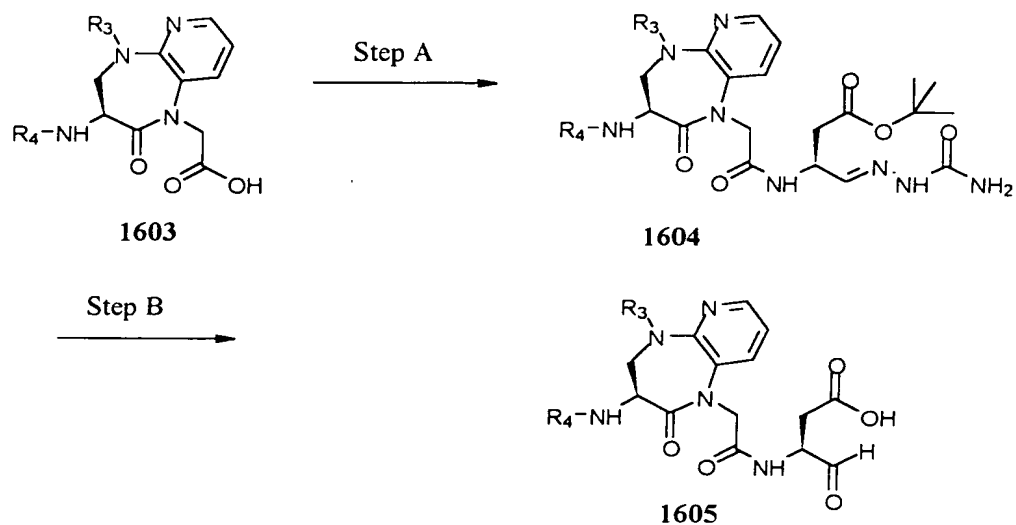
The reaction was concentrated *in vacuo*, the residue dissolved in 2 ml of H₂O and extracted with EtOAc (3x). The combined extracts were dried over Na₂SO₄ and concentrated *in vacuo*. Chromatography (flash, 5 SiO₂, 0 to 3% MeOH/CH₂Cl₂) gave 7.5 mg (3%) of **1600** as a light tan solid: ¹H NMR (CD₃OD) δ 7.96-7.92 (1H, d), 7.75-7.65 (1H, br. s), 7.14-7.08 (1H, d), 6.73-6.65 (1H, m), 5.83-5.75 (1H, br. s), 5.4-5.25 (1H, br. s), 4.6-4.5 (1H, m), 3.95-3.84 (1H, m), 3.55-10 3.48 (1H, m), 1.4 (9H, s)

Step E. **1601** is prepared from **1600** following the method in Step D for the preparation **600a/103**.



Synthesis of 1603. **1603** is prepared from **1601** following the methods for the synthesis of **603** from 15 **600**.

- 515 -



Synthesis of 1605. 1605 is prepared from 1603 by methods described for the synthesis of 605 from 603.

Table 15

	1605	R₃	R₄
5	a	PhCH ₂ CH ₂ CO	PhCO
	b	PhCH ₂ CO	PhCO
	c	PhCO	PhCO
	d	CH ₃ CO	PhCO
	e	CH ₃ OCH ₂ CO	PhCO
10	f	(CH ₃) ₂ CHCH ₂ CO	PhCO
	g	CH ₃ COCH ₂ CO	PhCO
	h	CH ₃ OCOCO	PhCO
	i	CH ₃ COCO	PhCO
	j	CH ₃ OCO	PhCO
15	m	CH ₃ SO ₃	PhCO
	n	CH ₃ CO	Naphthyl-2-CO
	p	PhCH ₂ NHCO	PhCO

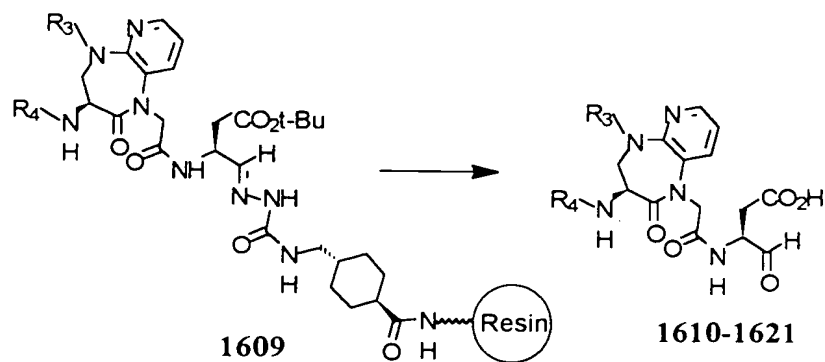
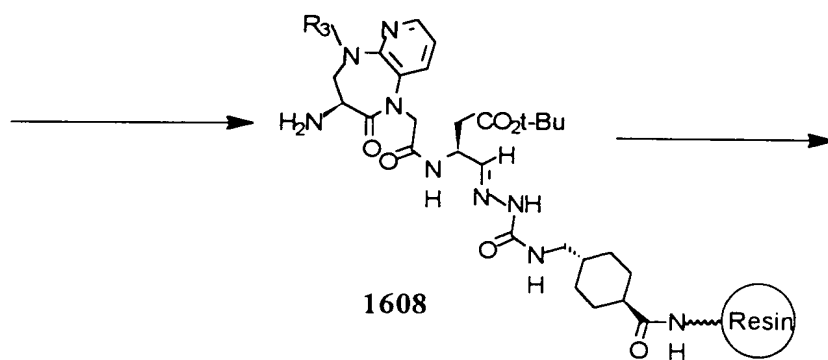
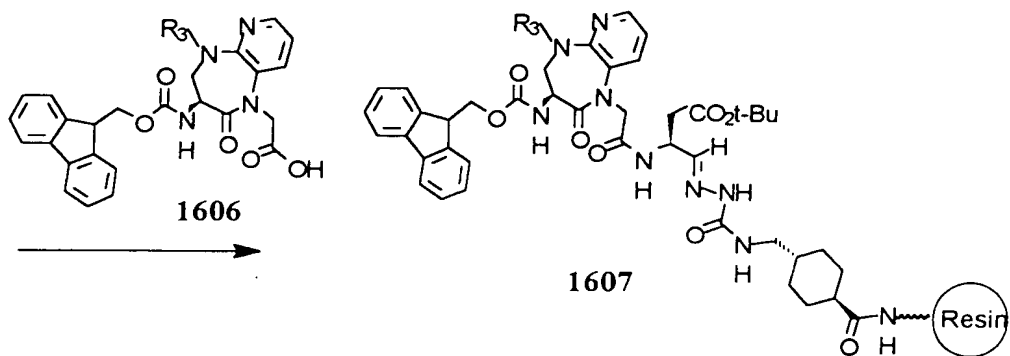
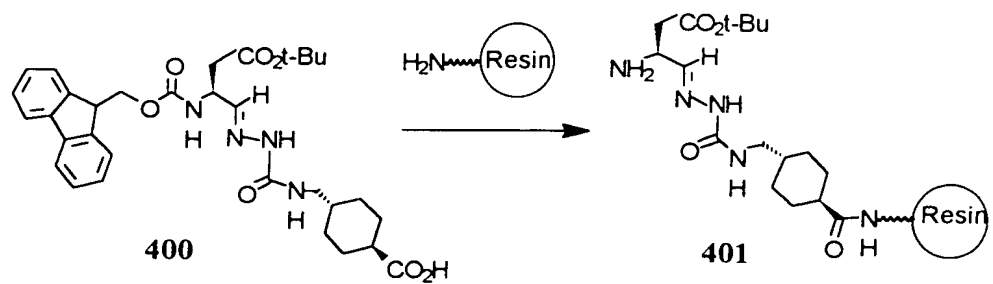
- 516 -

t	3-CH ₃ PhCH ₂ CO	PhCO
v	PhCH ₂ CH ₂ CO	PhCH ₂

Example 15

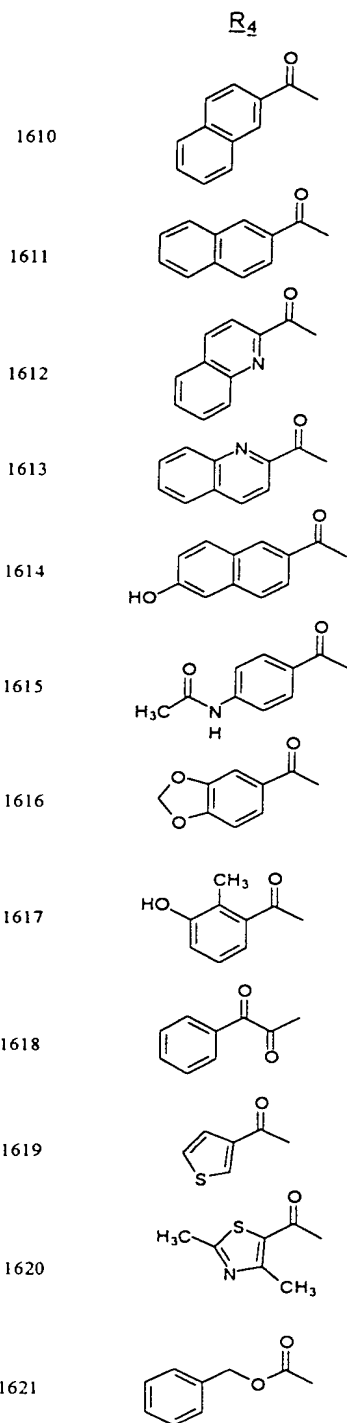
Compounds **1610-1621** are prepared from **1600**
5 by methods similar to the methods used to prepare
compounds **619-635** from **600a/103** and **600b**.

- 517 -



- 518 -

wherein for compounds 1610-1621,

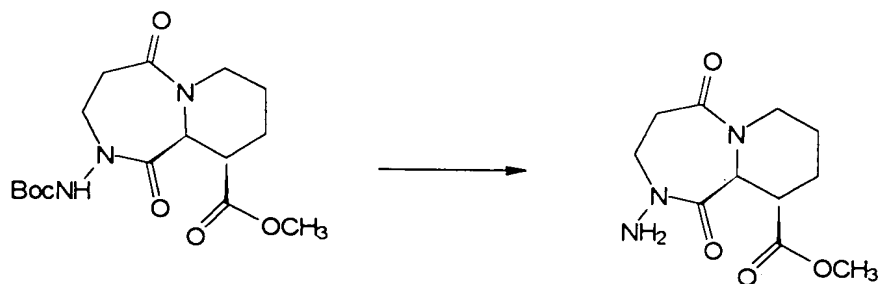
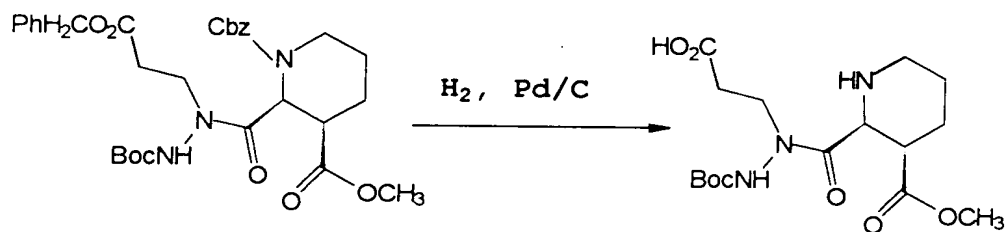
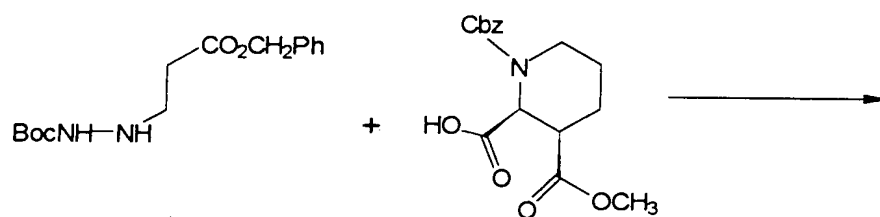
a $R_3 = \text{CH}_3\text{C}(\text{O})-$ b $R_3 = \text{CH}_3\text{OCH}_2\text{C}(\text{O})-$ 

- 519 -

Example 16

Compounds comprising scaffolds (e11), (y1), (y2), (z), and (e12) may be synthesized as described below.

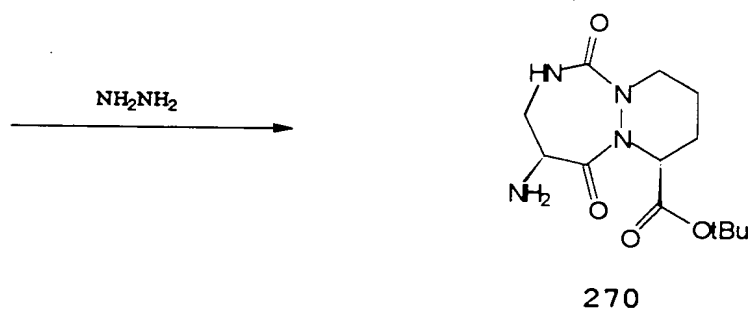
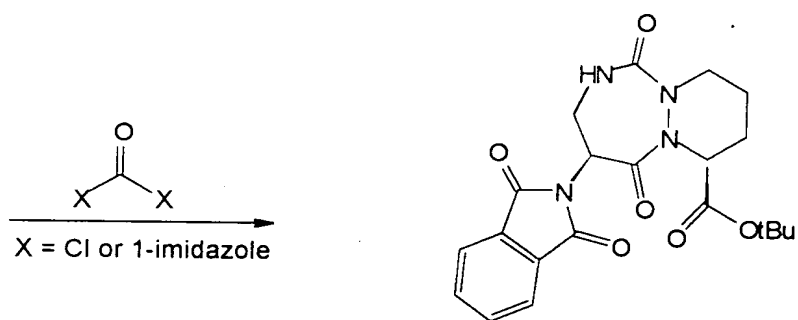
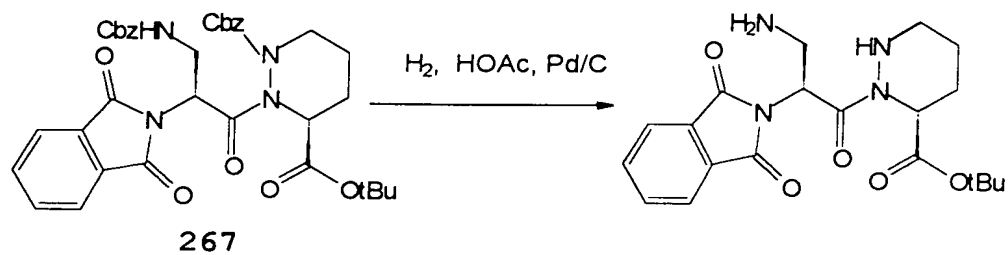
- 5 **Synthesis of Scaffold R_1** , wherein R_1 is (e11) and wherein Y_2 is =O.



269

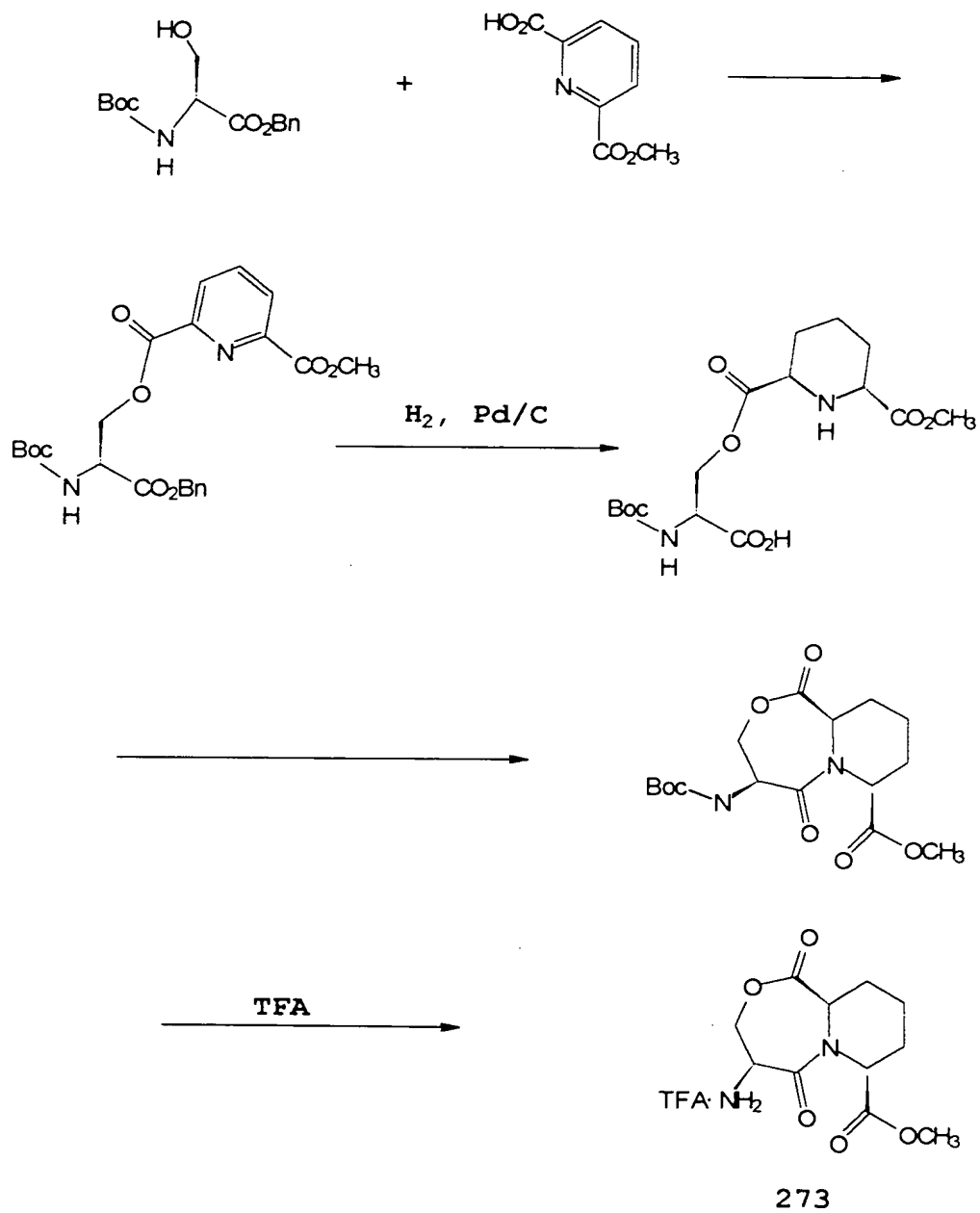
- 520 -

Synthesis of Scaffold R_1 , wherein R_1 is (y1) and wherein Y_2 is =O.



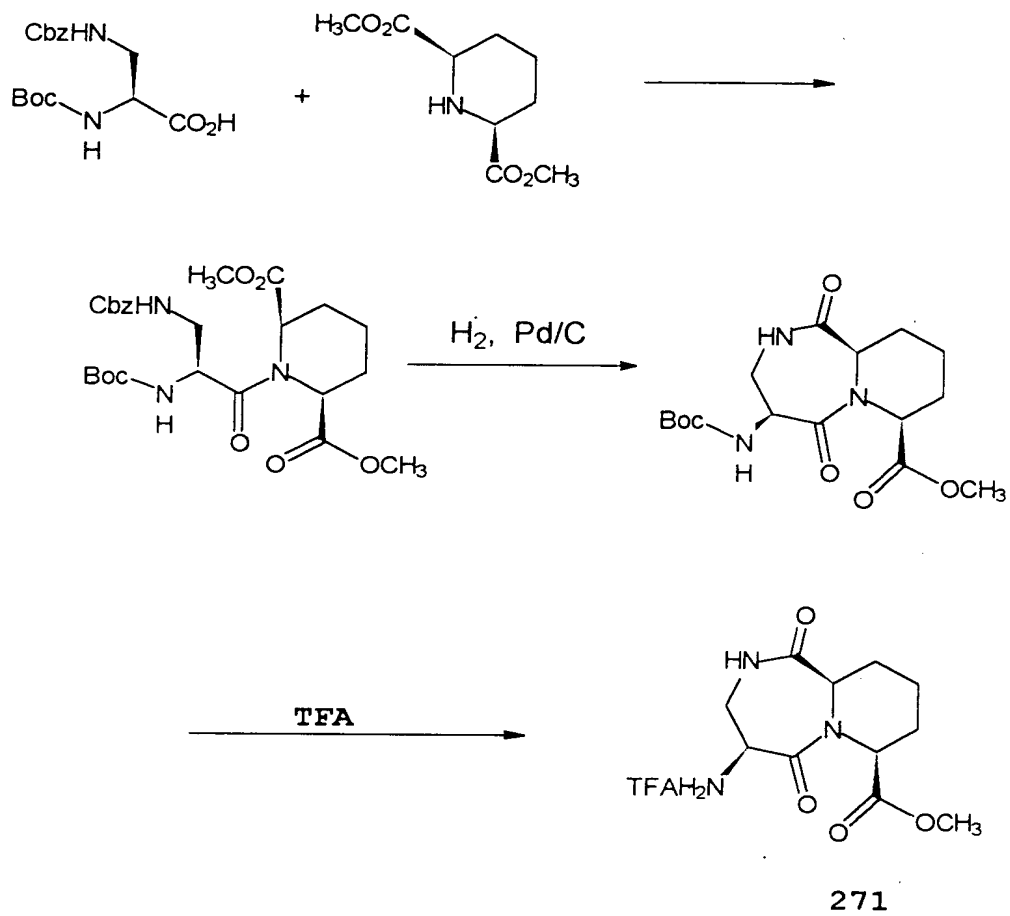
- 521 -

Synthesis of Scaffold R_1 , wherein R_1 is (y2) and wherein Y_2 is H_2 and X_7 is O.



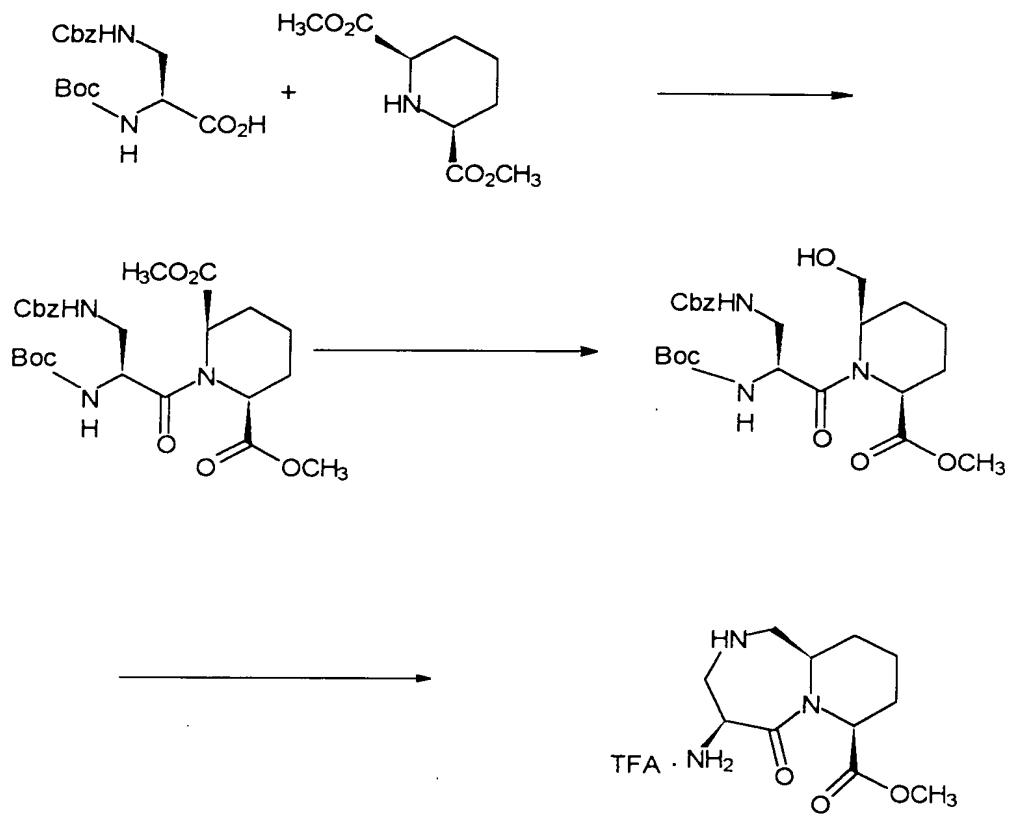
- 522 -

Synthesis of Scaffold R_1 , wherein R_1 is (y2) and wherein Y_2 is =O and X_7 is NH.



- 523 -

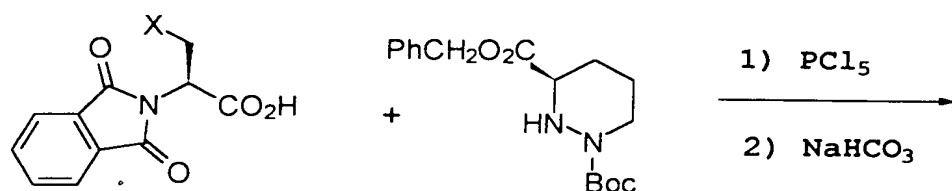
Synthesis of Scaffold R_1 , wherein R_1 is (y2) and wherein Y_2 is H_2 and X_7 is NH .



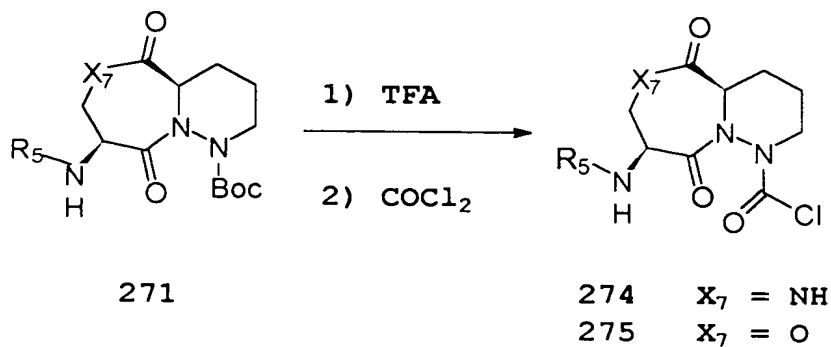
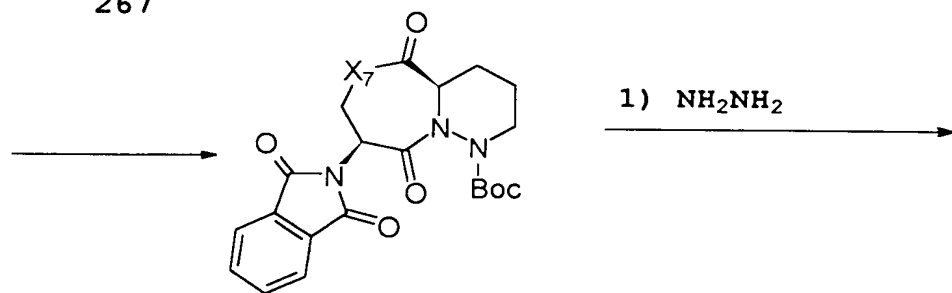
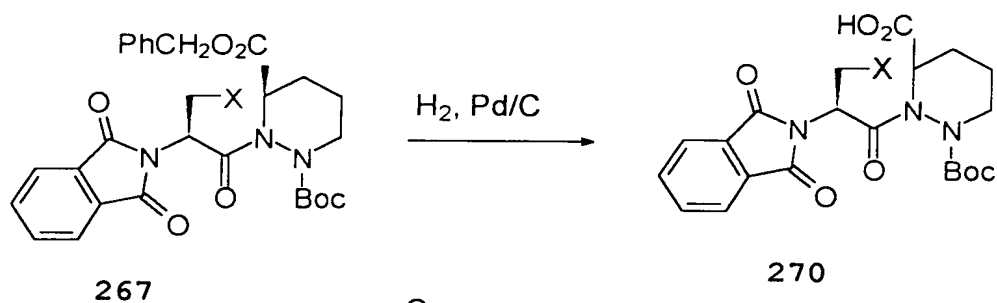
272

- 524 -

Synthesis of Scaffold R_1 , wherein R_1 is (z) and wherein Y_2 is O.



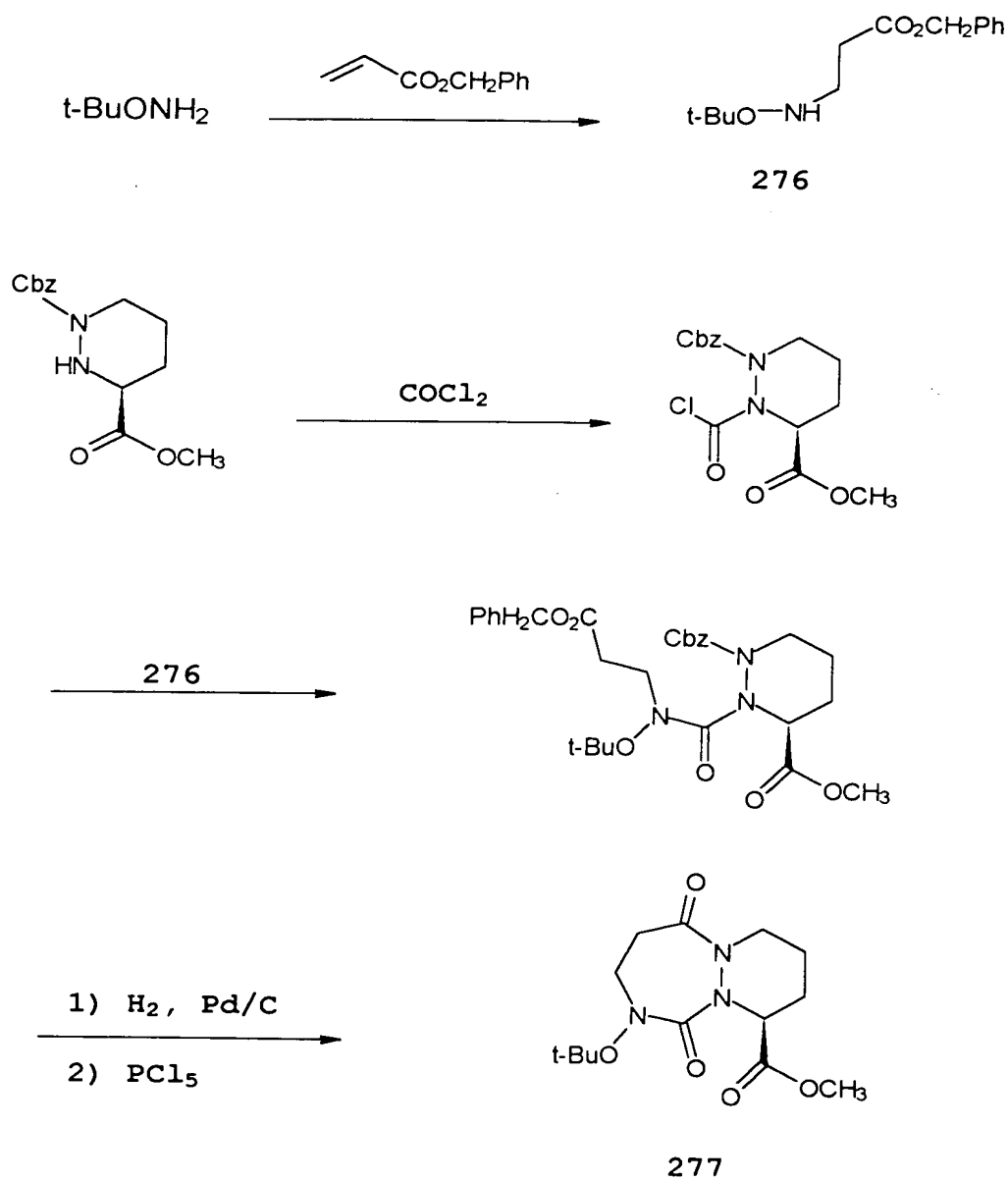
$X = \text{NHCBz}$
 $X = \text{OCH}_2\text{Ph}$



274 $X_7 = \text{NH}$
 275 $X_7 = \text{O}$

- 525 -

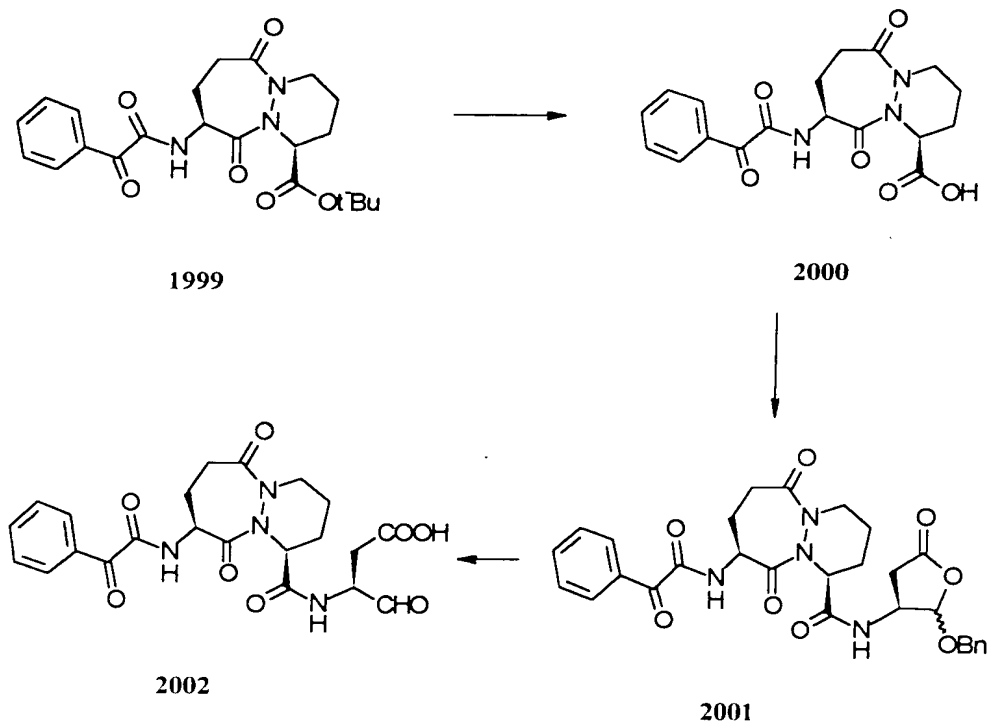
Synthesis of Scaffold R_1 , wherein R_1 is (e12) and wherein Y_2 is =O.



- 526 -

Example 17

The preparation of compounds 2001, 2002, 2100a-e, and 2201 is described below.



(1*S*,9*S*) 9-Benzoylformylamino-6,10-dioxo-
 5 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a]-[1,2]
 diazepine-1-carboxylic acid (2000). To a solution of
 t-butyl 9-amino-6,10-dioxo-1,2,3,4,7,8,9,10-
 octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-
 carboxylate (GB 2,128,984; 340 mg, 1.15 mmol) in
 10 CH₂Cl₂ was added benzoylformic acid (260 mg, 1.7
 mmol), HOBT (230 mg, 1.7 mmol) and EDC (340 mg, 1.7
 mmol). The resulting mixture was stirred at ambient
 temperature for 16 hours, poured into 1N HCl and
 extracted with CH₂Cl₂. The organic extracts were

- 527 -

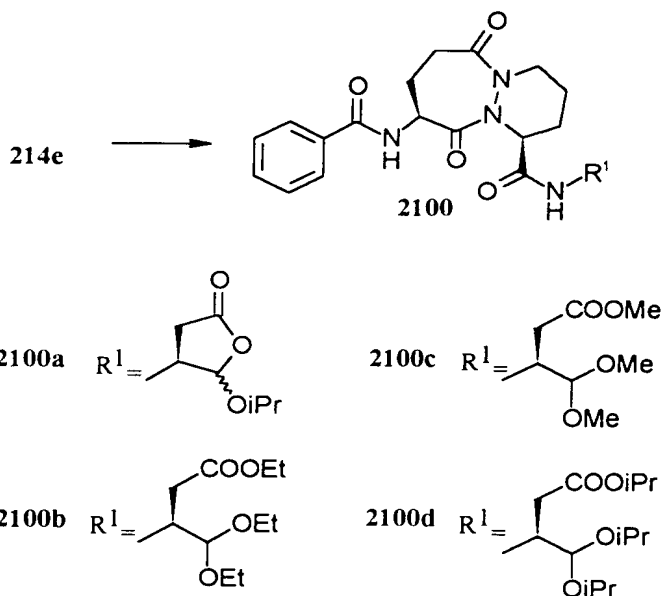
further washed with saturated NaHCO_3 , dried over MgSO_4 and concentrated to afford **1999** as a pale yellow solid. The solid was dissolved in CH_2Cl_2 (25 ml) and TFA (25 ml) and stirred overnight and
5 concentrated in vacuo to give 560 mg of **2000** as an oil.

[1*S*,9*S*(2*RS*,3*S*)] 9-Benzoylformylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-*N*-(2(*R,S*)-benzyloxy-5-oxotetrahydrofuran-3-yl)-6*H*-pyridazino[1,2-*a*][1,2]-
10 diazepine-1-carboxamide (**2001**), was synthesized from **2000** by methods similar to compound **213e** to afford 410 mg (63%) of **2001** as a white solid: ^1H NMR (CDCl_3 ; mixture of diastereomers) δ 8.25 (1*H*, d), 8.23 (1*H*, d), 7.78 (1*H*, dd), 7.65 (1*H*, bm), 7.50 (2*H*,
15 m), 7.40-7.25 (4*H*, m), 6.55 (1*H*, d), 5.57 (1*H*, d), 5.10 (1*H*, t), 5.05-4.95 (2*H*, m), 4.90, (1*H*, d), 4.80 (1*H*, d), 4.72 (1*H*, bm), 4.65 (1*H*, m), 4.55 (1*H*, m), 4.45 (1*H*, t), 3.25 (1*H*, m), 3.15 (1*H*, m), 3.00 (2*H*,
bm), 2.90 (1*H*, dd), 2.70 (1*H*, m), 2.47 (1*H*, dd), 2.45
20 (1*H*, m), 2.35 (1*H*, m), 2.00-1.75 (4*H*, m), 1.60 (1*H*, bm).

[3*S*(1*S*,9*S*)] 3-(9-Benzoylformylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino[1,2-*a*][1,2]-diazepine-1-carboxamido)-4-oxobutanoic acid (**2002**).
25 Compound **2001** (58.6 mg, 0.10 mmol) was treated with 15 ml of TFA/MeCN/water (1:2:3) and stirred at room temperature for 6.5 h. The reaction was extracted with ether. The aqueous layer was concentrated with azeotropic removal of the water using MeCN. The
30 product was suspended in CH_2Cl_2 , concentrated in vacuo and precipitated with ether to give 46.8 mg

- 528 -

(99%) of 2002 as a white solid: ^1H NMR (CD_3OD) δ
 9.05 (0.25H, d), 8.15 (1H, d), 7.68 (1H, t), 7.64
 (0.25H, d), 7.55 (3H, t), 7.35 (0.5H, m), 5.22 (1H,
 t), 4.90 (1H, m), 4.58 (1H, dd), 4.50 (1H, m), 4.28
 5 (1H, bm), 3.45 (1H, m), 3.10 (1H, bt), 2.68 (1H,
 ddd), 2.60-2.45 (2H, m), 2.30 (1H, dd), 2.15-2.05
 (2H, m), 1.90 (2H, bm), 1.68 (1H, bm).



Sub
A20

[1S,9S(2RS,3S)] 9-Benzoylamino-6,10-dioxo-
 1,2,3,4,7,8,9,10-octahydro-N-(2-isopropoxy-5-oxo-
 10 tetrahydro-furan-3-yl)-6H-pyridazino-
 [1,2-a][1,2]diazepine-1-carboxamide (2100a). A
 solution of 214e (101 mg, 0.23 mmol) in isopropanol
 (10 ml) was stirred at room temperature with a
 catalytic amount of *p*-toluenesulfonic acid (10 mg).
 15 After 75 minutes, the reaction mixture was poured
 into saturated NaHCO_3 and extracted with CH_2Cl_2 . The
 combined extracts were dried over Na_2SO_4 and

- 529 -

Sub
A20

concentrated. Flash chromatography (SiO₂, CH₂Cl₂ to EtOAc) afforded 56 mg (51%) of **2100a** as a white solid: ¹H NMR (CDCl₃; mixture of diastereomers) δ 7.9-7.8 (2H, m), 7.6-7.5 (1H, m), 7.5-7.4 (2H, m), 7.1 (0.5H, d), 6.9 (0.5H, d), 6.4 (0.5H, d), 5.6 (0.5H, d), 5.3 (0.5H, s), 5.2-5.1 (1H, m), 4.95 (0.5H, m), 4.75-4.5 (1.5H, m), 4.35 (0.5H, t), 4.1 (0.5H, m), 3.98 (0.5H, m), 3.3-2.75 (4H, m), 2.5-2.4 (2H, m), 2.25 (1H, m), 2.1-1.9 (3H, m), 1.75-1.55 (2H, m).

Sub
A21

10 **[3S(1S,9S)] 3-(9-Benzoylformylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-4,4-diethoxy-butyric acid, ethyl ester (2100b)**. A solution of **214e** (16 mg, 0.036 mmol) in ethanol (2 ml) was stirred at room temperature with a catalytic amount of *p*-toluenesulfonic acid (2 mg). After 5 days, the reaction mixture was poured into saturated NaHCO₃ and extracted with CH₂Cl₂. The combined extracts were dried over Na₂SO₄ and concentrated. Flash chromatography (SiO₂, CH₂Cl₂:EtOAc 95:5 v/v) afforded 16 mg (81%) of **2100b** as a white solid: ¹H NMR (CDCl₃) δ 7.85-7.74 (2H, m), 7.55-7.38 (3H, m), 7.04-6.95 (1H, d), 6.61-6.48 (1H, d), 5.15-5.08 (1H, m), 4.63-4.53 (1H, m), 4.52-4.45 (1H, m), 4.42-4.35 (1H, m), 4.15-4.05 (2H, m), 3.74-3.60 (2H, m), 3.57-3.42 (2H, m), 3.39-3.28 (1H, m), 3.03-2.93 (1H, m), 2.92-2.82 (1H, m), 2.65-2.52 (2H, m), 2.42-2.25 (1H, m), 2.20-1.88 (4H, m), 1.76-1.50 (2H, m), 1.35-1.10 (9H, m).

[3S(1S,9S)] 3-(9-Benzoylformylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-4,4-dimethoxy-butyric acid

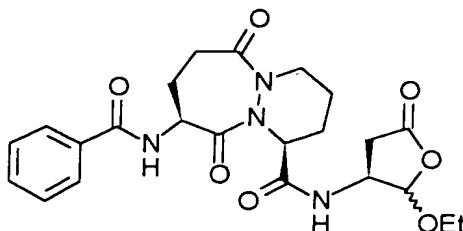
- 530 -

methyl ester (2100c). A solution of **214e** (165 mg, 0.37 mmol) in methanol (5 ml) was stirred at room temperature with a catalytic amount of *p*-toluenesulfonic acid (17.5 mg). After 4 days, the
5 reaction mixture was diluted with EtOAc and washed with 10% NaHCO₃ (3x) and brine. The combined extracts were dried over Na₂SO₄ and concentrated. Flash chromatography (SiO₂, EtOAc) afforded 127 mg (68%) of **2100c** as a white solid: ¹H NMR (CDCl₃) δ
10 7.82 (2H, d), 7.55-7.50 (1H, m), 7.47-7.43 (2H, m), 7.02 (1H, d), 6.53 (1H, d), 5.20-5.10 (1H, m), 4.56-4.50 (1H, m), 4.45-4.50 (1H each, two m), 3.69 (3H, s), 3.41 (3H, s), 3.43 (3H, s), 3.35-3.25 (1H, m), 3.06-2.98 (1H, m), 2.94-2.83 (1H, m), 2.65-2.53 (2H,
15 m), 2.35-2.32 (1H, m), 2.15-2.07 (1H, m), 2.00-1.89 (3H, m), 1.75-1.56 (2H, m).

**[3S(1S,9S)] 3-(9-Benzoylformylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-4,4-diisopropoxy-butyric
20 acid, isopropyl ester (2100d).** A solution of **214e** (53 mg, 0.12 mmol) in isopropanol (5 ml) was stirred at 50 °C with a catalytic amount of *p*-toluenesulfonic acid (5 mg). After 3 days the reaction mixture was poured into saturated NaHCO₃ and extracted with
25 CH₂Cl₂. The combined extracts were dried over Na₂SO₄ and concentrated. Flash chromatography (SiO₂, CH₂Cl₂:EtOAc (4:1 to 1:1 v/v)) afforded 49 mg (68%) of **2100d** as a white solid: ¹H NMR (CDCl₃) δ 7.85 (2H, d), 7.50-7.43 (1H, m), 7.41-7.35 (2H, m), 7.02 (1H, d), 6.47 (1H, d), 5.13-5.07 (1H, m) 5.00-4.9 (1H, m), 4.61-4.55 (2H, m), 4.37-4.30 (1H, m), 3.80-3.70 (1H, m), 3.90-3.80 (1H, m), 3.42-3.35 (1H, m),
30

- 531 -

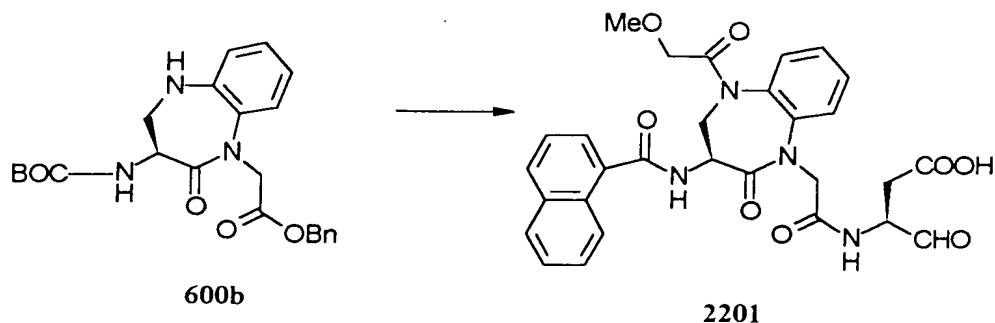
3.03-2.93 (1H, m), 2.91-2.81 (1H, m), 2.62-2.50 (2H, m), 2.38-2.33 (1H, m), 2.12-2.06 (1H, m), 1.97-1.81 (3H, m), 1.70-1.60 (2H, m), 1.28-1.05 (18H, m).



2100e

[1*S*,9*S*(2*RS*,3*S*)] 9-Benzoylamino-6,10-dioxo-
 5 1,2,3,4,7,8,9,10-octahydro-N-(2-ethoxy-5-oxo-
 tetrahydro-furan-3-yl)-6H-pyridazino[1,2-a][1,2]-
 diazepine-1-carboxamide (2100e), was synthesized from
 302 via methods used to synthesize 304a to afford
 2100e, except ethanol and triethylorthoformate were
 10 used instead of methanol and trimethylorthoformate.
 Chromatography (SiO₂, 5% ethanol/CH₂Cl₂) afforded 92
 mg (68%) of a white solid: ¹H NMR (CDCl₃; mixture of
 diastereomers) δ 7.90-7.80 (2H, m), 7.60-7.50 (1H,
 m), 7.50-7.40 (2H, m), 7.30 (0.5H, d), 7.00 (0.5H,
 15 d), 6.50 (0.5H, d), 5.50 (0.5H, d), 5.20-5.10 (1.5H,
 m), 4.95 (0.5H, m), 4.75-4.65 (0.5H, m), 4.65-4.50
 (1H, m), 4.38 (0.05H, t), 4.00-3.90 (0.5H, m), 3.85-
 3.75 (0.5H, m), 3.75-3.65 (0.5H, m), 3.65-3.55 (0.5H,
 m), 3.30-2.70 (4H, m), 2.50-2.35 (2H, m), 2.30 (1H,
 20 d), 2.15-1.90 (3H, m), 1.80-1.60 (2H, m), 1.25-1.20
 (3H, two t)

- 532 -



(3*S*)-3-[(3*S*)-2-oxo-3-(1-naphthoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid

(2201) was synthesized from 600b by the methods used
 5 to synthesize 605b to afford 2201: ^1H NMR (CDCl_3) δ
 8.30-8.22 (1*H*,m), 8.05-7.98 (1*H*, d), 7.96-7.83
 (1*H*,m), 7.77-7.68 (1*H*,m), 7.67-7.40 (7*H*,m), 5.12-5.02
 (1*H*,m), 4.98-4.41 (5*H*,m), 4.38-4.24 (1*H*,m), 4.07-4.00
 (1*H*,d), 3.92-3.80 (2*H*,m), 3.32 (3*H*,s), 2.75-2.60
 10 (1*H*,m), 2.58-2.35 (1*H*,m).

- 533 -

Example 18

We obtained the following data for selected compounds of this invention using the methods described herein (Table 16, see Example 7; Tables 17 and 18, see Examples 1-4). The structures and preparations of compounds of this invention are described in Examples 28-31.

Table 16 Comparison of Prodrugs for Efficacy in LPS Challenged Mice: Inhibition of IL-1 β Production.

The percent inhibition of IL-1 β production after treatment with a compound of the invention is shown as a function of time after LPS challenge ("-" indicates that no value was obtained at that relative time).

		Time of Compound Administration (relative to time of LPS challenge, PO, 50 mg/kg)			
	Compound	-2h	-1h	0h	+1h
	213f	(-4)	-	8	-
	213h	9	-	53	-
	213i	(-11)	-	62	-
20	213k	0	-	68	-
	213l	(-18)	-	80	-
	213m	26	-	42	-
	213o	4	-	8	-
	213p	21	-	29	-
25	213q	17	-	91	-
	213r	59	-	37	-
	213x	0	-	78	-
	213y	29	-	50	-
	214e	39	-	70	75
		43	44	48	11
		-	-	-	47
30	214k	12	-	31	-
	214l	0	-	54	-
	214m	0	-	17	-
	214w	11	-	91	-
	264l	0	-	23	-
35	404	-	-	-	56
		55	-	6	-

- 534 -

	Compound	-2h	-1h	0h	+1h
5	412	0	-	0	-
		11	-	37	-
	418	-	-	-	64
		25	-	52	-
	434	-	-	-	80
10		0	-	63	-
	450	0	-	35	-
	452	-	-	-	70
		28	-	89	-
	456	-	-	-	56
15		41	-	69	-
	470	0	-	36	-
	471	0	-	34	-
	475	0	-	15	-
	481	27	-	0	-
20	486	19	-	15	-
	487	17	-	20	-
	528	25	-	67	-
	550f	0	-	50	-
	550h	55	-	73	-
25	550i	(-10)	-	23	-
	550k	36	-	34	-
	550l	9	-	38	-
	550m	45	-	52	-
	550n	19	-	65	-
30	550o	19	-	64	-
	550p	30	-	60	-
	655	0	-	68	-
	656	31	-	16	-
	662	41	-	75	-
35	668	-	-	-	53
	695a	49	-	78	-
	1015	15	-	28	-
	2001	64	62	58	55
	2001a	10	-	16	-
	2002	5	-	87	-
	2100h	34	-	32	-
	2100i	19	-	74	-
	2100j	48	41	0	33
	2100k	30	50	32	72
	2100l	52	-	28	-
	2100m	40	-	42	-
	2100n	21	9	64	73
	2100o	31	44	68	64

- 535 -

Table 17 Data for selected compounds of this invention obtained using the methods described in Examples 1-4.

	Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
5	213f			3000		
	213g			2200		
	213h			1500		
	213i			1100		
	213j					
10	213k			2000		
	213l			2000		
	213m			2500		
	213o		5000	3300		
	213p			<300		
15	213q			<300		
	213r			<300		
	213v	0.5	1,100	1100	41	23
	213x		4500	2500		
	213y			930		
20	214j	4.2	2500	6000		
	214k	0.2	500	580		22
	214l	6	1900	1100		12
	214m	1.5	530	2200		33.4
	214w	0.6	620	370		15
25	246b	30000	>30000		87	
	264l			3000		
	265a	2600	25000			
	265c	1100	4500			32
	265d	500	1500			35
30	265f	1200				24
	280b		13000			
	280c		10000			86
	280d		25000			
	283b		1750			41
	283c		4000			50

- 536 -

	Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
	283d		>8000	10000		
	308c	3000				
	308d	3000				
5	500	25	1800	1800		
	501	2.5	1800	1600		
	505c		1500			
	505d		>20000			
	505f		550			
10	510a	65	200		267	
	510d	2300	>20000			
	511c	730	>20000		78	40
	528			2200		
	550f			1100		
	550h			1800		
15	550i			1400		
	550k			3000		
	550l			750		
	550m			2000		
	550n			<300		
20	550o		450	3000		
	550p			2900		
	550q			700		
	640	155	2250	3900		
	642	35	8000	2900		
25	645	150				
	650	550	4000			
	653	30	2300	6000		
	655					
	656	0.6	2100	1600		2.9
30	662	0.5	1800	800		2.75
	668	9	5200	3700		29
	669	14		10000		
	670			4500		
35	671	5	2000	2500		33.2
	677			610		
	678	5	2700	2200		
	680					

- 537 -

	Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
	681	9	3000	5000		
	682			1300		
	683	400	>20000	>20000		
	684	15	5000	2800		
5	686	4	4000	9000		
	688a			3000		
	688b			1300		
	689a	0.8	910	2500		
	689b	2.2	600	2000		
10	690a			1600		
	690b					
	691a	2.1	2900	1200		9.9
	691b	11.5	1,900	1400		
	692a					
15	692b			1800		
	693					
	694	3	2600	2100		
	695a					
	695b					
20	695c			2500		
	696	4.5	2000	2900		13
	700	275				
	701	90				
	702	45	>5000	20000		
25	703	5	1400	20000		
	704	30	2600	9800		
	705	5	2300	3200		
	706	5	2400	5800		
	707	180				
30	708	140				
	709	10	2100	14000		
	710	110				
	711	175				
	910	10	3400	3800		
35	911	9	3500	1900		
	912	10	4200	3800		
	913	4.5	2400	7000		

- 538 -

	Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
5	914	5.2	2600	2800		
	915	11.5	>8000	1900		
	918	7		1150		
	919	4	2000	4300		
	920	16	2100	3000		
10	921	8.5	1800	3000		
	1018	170	4000	5500		9.1
	1052	100	2500			16
	1053	27	2000	>20000		34
	1056	170				17
15	1075	120	5000	5500		14.5
	1095	360	6000			28
	1105	250	3500	3000		
	1106	75	4000	1700		
	1107	65				
20	1108	22	1400	2600		
	1109	80				
	1110	45				
	1111	18	6050	4400		
	1112	3.5	1800	2300		
25	1113	290				
	1114	125				
	1115	250				
	1116	215				
	1117	35	1700	1300		
30	1118	380				
	1119	515				
	1120	95				
	1121	170				
	1122	400				
35	1123	30	2,400	4500		
	1124	270				
	1125	55	2300	9000		
	2001a			3000		
	2100f					
	2100g					
	2100h			2000		

- 539 -

5

Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
2100i					
2100j	30000		12000		
2100k	520	4000	600		
2100l		750	2200		
2100m					
2100n	670	770	4000		
2100o	670	1150	1500		

10 We obtained the following data for selected compounds of this invention (Table 18) using the methods described herein (see Examples 1-4). The structures and preparations of compounds of this invention are described in Examples 28-31.

Table 18

15

Cmpd.	Fluorescent Assay kinact $m^{-1} s^{-1}$	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
286	370000	300	1600		119
505 b	190000	1500	2100	161	196
505 e	420000	9000	1000		

Example 19

20 In vivo acute assay for efficacy as anti-inflammatory agent

Results in the Table 19 show that 412f, 412d and 696a inhibit IL-1 β production in LPS-challenged mice after oral administration using ethanol/PEG/water,

- 540 -

β -cyclodextrin, labrosol/water or cremophor/water as vehicles. The compound was dosed at time of LPS challenge. The protocol is described in Example 7.

5 Table 19 Inhibition (%) of IL-1 β production in LPS-challenged mice.

Compound	10 mg/kg dose	25 mg/kg dose	50 mg/kg dose
412f	17%	25%	32%
412e	5%	17%	61%
696a	0	45%	52%

10

Example 20

Mouse Carrageenan Peritoneal Inflammation

Inflammation was induced in mice with an intraperitoneal (IP) injection of 10 mg carrageenan in 0.5 ml of saline (Griswold et al., Inflammation, 13, pp. 727-739 (1989)). Drugs are administered by oral gavage in ethanol/PEG/water, β -cyclodextrin, labrosol/water or cremophor/water vehicle. The mice are sacrificed at 4 hours post carrageenan administration, then injected IP with 2 ml of saline containing 5U/ml heparin. After gentle massage of the peritoneum, a small incision is made, the contents collected and volume recorded. Samples are kept on ice until centrifuged (130 x g, 8 mins at 4 °C) to remove cellular material, and the resultant supernatant stored at -20 °C. IL-1 β levels in the peritoneal fluid are determined by ELISA.

Results in the Table 20 show prodrug **412f** inhibits IL-1 β production in carrageenan-challenged mice after oral administration of drug. Compound **214e**

- 541 -

did not inhibit IL-1 β production when dosed orally at 50 mg/kg.

Table 20 Inhibition (%) of IL-1 β production by **412f** and **412d** in carrageenan-challenged mice.

Dose (mg/kg)	Compound 412f	Compound 412d
1	30%	0
10	54%	32%
25	49%	31%
50	73%	36%
100	75%	53%

Example 21

Type II Collagen-induced Arthritis

Type II collagen-induced arthritis was established in male DBA/1J mice at described Wooley and Geiger (Wooley, P.H., Methods in Enzymology, 162, pp. 361-373 (1988) and Geiger, T., Clinical and Experimental Rheumatology, 11, pp. 515-522 (1993)).

Chick sternum Type II collagen (4 mg/kg in 10 mM acetic acid) was emulsified with an equal volume of Freund's complete adjuvant (FCA) by repeated passages (400) between two 10 ml glass syringes with a gauge 16 double-hub needle. Mice were immunized by intradermal injection (50 μ l; 100 μ l CII per mouse) of collagen emulsion 21 days later at the contra-lateral side of the tail base. Drugs were administered twice a day (10, 25 and 50 mg/kg) by oral gavage approximately 7 h apart. Vehicles used included ethanol/PEG/water, β -cyclodextrin, labrosol/water or cremophor/water. Drug treatments were initiated within 2 h of the CII booster

- 542 -

immunization. Inflammation was scored on a 1 to 4 scale of increasing severity on the two front paws and the scores are added to give the final score.

Results in the **Figs. 12, 13 and 14** show
5 prodrugs **412f**, **412d** and **696a** inhibit inflammation in collagen-induced arthritits in mice after oral administration. Compound **214e** did not inhibit inflammation when dosed (50 mg/kg) once a day by oral gavage.

10

Example 22

In vivo bioavailability determination

The drugs (10-100 mg/kg) were dosed orally to rats (10 mL/kg) in ethanol/PEG/water, β -cyclodextrin, labrosol/water or cremophor/water. Blood samples were
15 drawn from the carotid artery at 0.25, 0.50, 1, 1.5, 2, 3, 4, 6, and 8 hours after dosing, centrifuged to plasma and stored at -70°C until analysis. Aldehyde concentrations were determined using an enzymatic assay. Pharmacokinetic analysis of data was performed
20 by non-linear regression using RStrip (MicroMath Software, UT). Drug availability values were determined as follows: (AUC of drug after oral prodrug dosing/AUC of drug after i.v. dosing of drug)x(dose i.v./dose p.o.) x100%.

25

Results in Table 21 show that prodrugs **412f**, **412d** and **696a** give significant blood levels of drug and have good drug availability when dosed orally. Blood levels of **214e** were not detected when it was dosed orally.

- 543 -

Table 21 Oral Bioavailability of **412f**, **412d**, **696a** and **214e** in Rat.

Compound	Dose (mg/kg)	Cmax (μ g/ml)	Drug Availability (%)
412f	25	2.4	32
412d	25	2.6	35
696a	50	1.2	10
214e	45	0.2	0.9%

Example 23

ICE cleaves and activates pro-IGIF

10 ICE and ICE homolog expression plasmids

A 0.6 kb cDNA encoding full length murine pro-IGIF (H. Okamura et al., *Nature*, 378, p. 88 (1995)) was ligated into the mammalian expression vector pCDLSR α (Y. Takebe et al., *Mol. Cell Biol.*, 8, p. 466 (1988)).

Generally, plasmids (3 μ g) encoding active ICE (above), or the three ICE-related enzymes TX, CPP32, and CMH-1 in the pCDLSR α expression vector (C. Faucheu et al., *EMBO*, 14, p. 1914 (1995); Y. Gu et al., *EMBO*, 14, p. 1923 (1995); J. A. Lippke et al., *J. Biol. Chem.*, 271, p. 1825 (1996)), were transfected into subconfluent monolayers of Cos cells in 35-mm dishes using the DEAE-dextran method (Y. Gu et al., *EMBO J.*, 14, p. 1923 (1995)). Twenty-four hours later, cells were lysed and the lysates subjected to SDS-PAGE and immunoblotting using an antiserum specific for IGIF (H. Okamura et al., *Nature*, 378, p. 88 (1995)).

Polymerase chain reaction was used to introduce Nde I sites at the 5' and 3' ends of the murine pro-IGIF cDNA using the following primers: GGAATTCCATATGGCTGCCATGTCAGAAGAC (forward) and GGTTAACCATATGCTAACTTTGATGTAAGTTAGTGAG (reverse). The

- 544 -

resulting NdeI fragment was ligated into E. coli expression vector pET-15B(Novagen) at the NdeI site to create a plasmid that directs the synthesis of a polypeptide of 213 amino acids consisting of a 21-residue peptide (MGSSHHHHHSSGLVPRGSHM, where LVPRGS represents a thrombin cleavage site) fused in-frame to the N-terminus of pro-IGIF at Ala2, as confirmed by DNA sequencing of the plasmid and by N-terminal sequencing of the expressed proteins. E. coli strain BL21(DE3) carrying the plasmid was induced with 0.8 mM isopropyl-1-thio- β -D-galactopyranoside for 1.5 hours at 37°C, harvested, and lysed by microfluidization (Microfluidic, Watertown, MA) in Buffer A (20 mM sodium phosphate, pH 7.0, 300 mM NaCl, 2 mM dithiothreitol, 10% glycerol, 1 mM phenylmethylsulfonyl fluoride, and 2.5 μ g/ml leupeptin). Lysates were cleared by centrifugation at 100,000 x g for 30 min. (His)6-tagged pro-IGIF protein was then purified from the supernatant by Ni-NTA-agarose (Qiagen) chromatography under conditions recommended by the manufacturer.

In Vitro pro-IGIF Cleavage Reactions

In vitro cleavage reactions (30 μ l) contained 2 μ g of purified pro-IGIF and various concentrations of the purified proteases in a buffer containing 20 mM Hepes, pH 7.2, 0.1% Triton X-100, 2 mM DTT, 1 mM PMSF and 2.5 μ g/ml leupeptin and were incubated for 1 hour at 37°C. Conditions for cleavage by granzyme B were as described previously (Y. Gu et al., J. Biol. Chem., 271, p. 10816 (1996)). Cleavage products were analyzed by SDS-PAGE on 16% gels and Coomassie Blue staining, and were subjected to N-terminal amino acid sequencing

- 545 -

using an ABI automated peptide sequencer under conditions recommended by the manufacturer.

Kinetic Parameters of IGIF Cleavage by ICE

The kinetic parameters (k_{cat}/K_M , K_M , and k_{cat}) for IGIF cleavage by ICE were determined as follows. ³⁵S-methionine-labeled pro-IGIF (3000 cpm, prepared by *in vitro* transcription and translation using, the TNT T7-coupled reticulocyte lysate system (Promega) and pro-IGIF cDNA in a pSP73 vector as template) were incubated in reaction mixtures of 60 μ l containing 0.1 to 1 nM recombinant ICE and 190 nM to 12 μ M of unlabeled pro-IGIF for 8-10 min at 37°C. Cleavage product concentrations were determined by SDS-PAGE and PhosphoImager analyses. The kinetic parameters were calculated by nonlinear regression fitting of the rate vs. concentration data to the Michaelis-Menten equation using the program Enzfitter (Biosoft).

IFN- γ Induction Assays

A.E7 Th1 cells (H. Quill and R. H. Schwartz, *J. Immunol.*, 138, p. 3704 (1987)) (1.3×10^5 cells in 0.15 ml Click's medium supplemented with 10% FBS, 50 μ M 2-mercaptoethanol and 50 units/ml IL-2) in 96-well plates were treated with IGIF for 18-20 hours and the culture supernatant were assayed for IFN- γ by ELISA (Endogen, Cambridge, MA).

Example 24

Processing of pro-IGIF by ICE In Cos Cells

Cos cells were transfected with various expression plasmid combinations as described in Example 23. Transfected Cos cells (3.5×10^5 cells in a 35-mm dish) were labeled for 7 hours with 1 ml of methionine-

- 546 -

free DMEM containing 2.5% normal DMEM, 1% dialyzed fetal bovine serum and 300 $\mu\text{Ci/ml}$ ^{35}S -methionine (^{35}S -Express Protein Labeling-Mix, New England Nuclear). Cell lysates (prepared in 20 mM Hepes, pH 7.2, 150 mM NaCl, 0.1% Triton X-100, 5 mM N-ethylmaleimide, 1 mM PMSF, 2.5 $\mu\text{g/ml}$ leupeptine) or conditioned medium were immunoprecipitated with an antiIGIF antibody that recognizes both the precursor and the mature forms of IGIF (H. Okamura et al., Nature, 378, p. 88 (1995)). Immunoprecipitated proteins were analyzed by SDS-PAGE (polyacrylamide gel electrophoresis) and fluorography (Fig. 2A).

We also measured the presence of IFN- γ inducing activity in the cell lysates and the conditioned media of transfected cells (Fig. 2B). Transfected Cos cells (3.5×10^5 cells in a 35-mm dish) were grown in 1 ml medium for 18 hours. Media was harvested and used at 1:10 final dilution in the IFN- γ induction assay (Example 23). Cos cell pellets from the same transfection were lysed in 100 μl of 20 mM Hepes, pH 7.0, by freeze-thawing 3 times. Lysates were cleared by centrifugation as described above and were used at a 1:10 dilution in the assay.

Example 25

IGIF is a physiological substrate of ICE

Wild type (ICE+/+) and ICE-/- mice were primed with heat-inactivated *P. acnes*, and Kupffer cells were isolated from these mice 7 days after priming and were then challenged with 1 $\mu\text{g/ml}$ LPS for 3 hours. The amounts of IGIF in the conditioned media were measured by ELISA.

- 547 -

Wild type or ICE-deficient mice were injected intraperitoneally with heat-killed p. acnes as described (H. Okamura et al., Infection and Immunity, 63, p. 3966 (1995)). Kupffer cells were prepared seven
5 days later according to Tsutsui et al. (H. Tsutsui et al., Hepato-Gastroenterol., 39, p. 553 (1992)) except a nycodenz gradient was used instead of metrizamide. For each experiment, Kupffer cells from 2-3 animals were pooled and cultured in RPMI 1640 supplemented with 10%
10 fetal calf serum and 1 µg/ml LPS. Cell lysates and conditioned medium were prepared 3 hours later.

Kupffer cells from wild type and ICE-/- mice were metabolically labeled with ³⁵S-methionine as for Cos cells (described above in Example 24) except that
15 methionine-free RPMI 1640 was used in place of DMEM. IGIF immunoprecipitation experiments were performed on cell lysates and conditioned media and immunoprecipitates were analyzed by SDS-PAGE and fluorography as described in Example 23. See Fig. 3.

20

Example 26

Induction of IFN-γ Production In Vivo

LPS mixed with 0.5% carboxymethyl cellulose in PBS, pH 7.4, was administered to mice by intraperitoneal injection (30 mg/kg LPS) in a dose
25 volume of 10 ml/kg. Blood was collected every 3 h for 24 h from groups of three ICE-deficient or wild type mice. Serum IFN-γ levels were determined by ELISA (Endogen).

- 548 -

Example 27

IGIF and IFN- γ Inhibition Assays

Inhibition of IGIF processing by ICE inhibitors was measured in ICE inhibition assays as described herein (see Example 1 and Table 22).

Human PBMC Assays

Human buffy coat cells were obtained from blood donors and peripheral blood mononuclear cells (PBMC) were isolated by centrifugation in LeukoPrep tubes (Becton-Dickinson, Lincoln Park, NJ). PBMC were added (3×10^6 /well) to 24 well Corning tissue culture plates and after 1 hr incubation at 37°C, non-adherent cells were removed by gently washing. Adherent mononuclear cells were stimulated with LPS (1 μ g/ml) with or without ICE inhibitor in 2 ml RPMI-1640-10% FBS. After 16-18 hr incubation at 37°C, IGIF and IFN- γ were quantitated in culture supernatants by ELISA.

For example, we obtained the following data for compound **412** of this invention using the methods described herein. The structure of compound **412** is shown below.

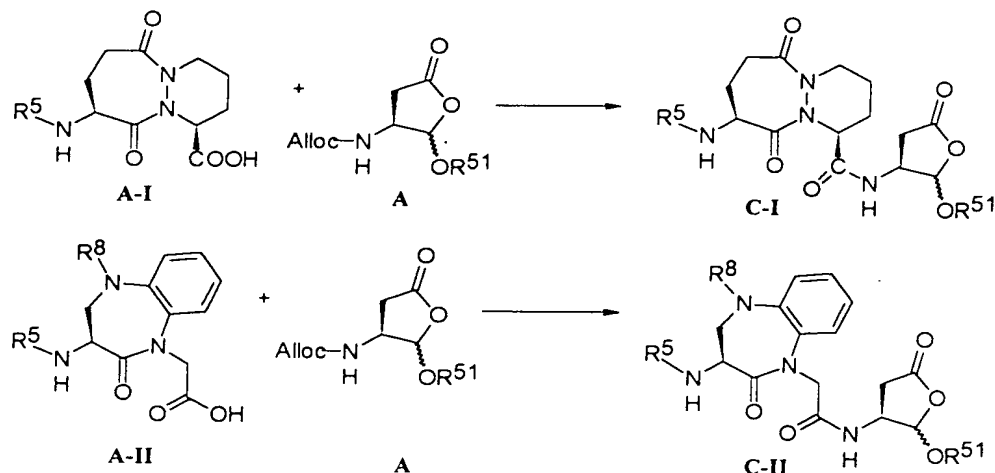
Table 22

compound	UV-Visible K_i (nM)	Cell PBMC avg. IC50 (nM)
412	1.3	580

- 549 -

Example 28

Compounds of this invention may be prepared via various methods. The following illustrates a preferred method:



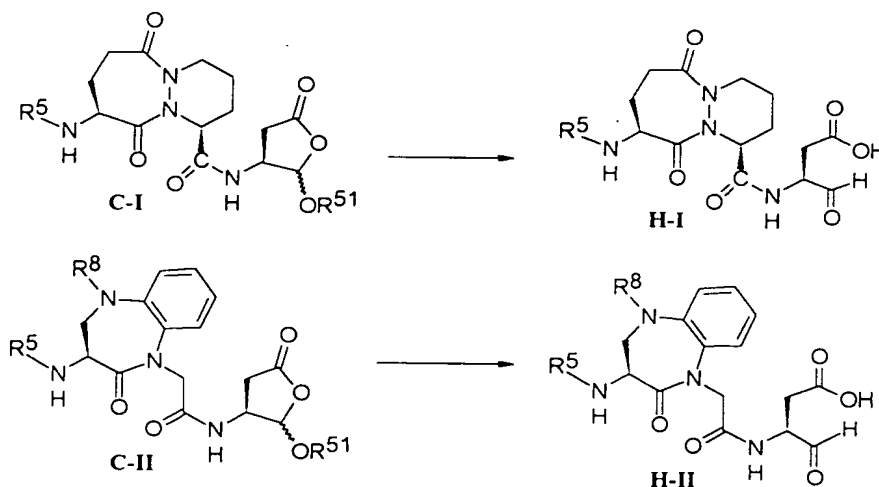
5 To a solution of **A** (1.1 equivalent) in CH₂Cl₂ (or DMF, or CH₂Cl₂:DMF (1:1)) is added triphenylphosphine (0-0.5 equivalent), a nucleophilic scavenger (2-50 equivalents) and tetrakis-
 10 triphenylphosphine palladium(0) (0.05-0.1 equivalent) at ambient temperature under inert atmosphere (nitrogen or argon). After 10 minutes, the above reaction mixture is optionally concentrated, then a solution of acid **A-I** or **A-II** in CH₂Cl₂ (or DMF, or CH₂Cl₂:DMF (1:1)) is added followed by addition of HOBT (1.1 equivalent)
 15 and EDC (1.1 equivalent). The resulting reaction mixture is allowed to stir at ambient temperature 1 hour-48 hours to provide coupled products **C-I** or **C-II**.

Various nucleophilic scavengers may be used in the above process. Merzouk and Guibe, Tetrahedron Letters, 33, pp. 477-480 (1992); Guibe and Balavoine, Journal of Organic Chemistry, 52, pp. 4984-4993

- 550 -

(1987)). Preferred nucleophilic scavengers that may be used include: dimedone, morpholine, trimethylsilyl dimethylamine and dimethyl barbituric acid. More preferred nucleophilic scavengers are trimethylsilyl dimethylamine (2-5 equivalents) and dimethyl barbituric acid (5-50 equivalents). When the nucleophilic scavenger is trimethylsilyl dimethylamine, the above reaction mixture must be concentrated prior to addition of A-I or A-II.

10 Other compounds of this invention may be prepared by hydrolyzing compounds represented by C-I and C-II to compounds represented by H-I and H-II as described in the following scheme:



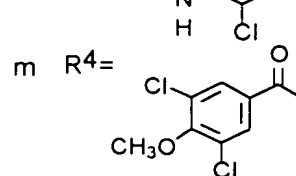
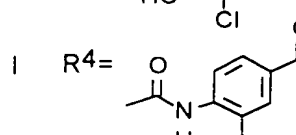
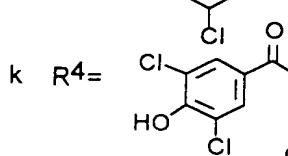
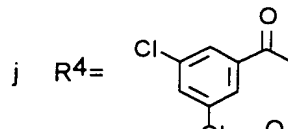
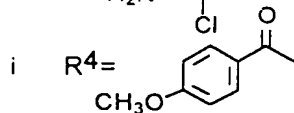
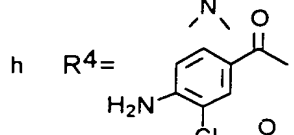
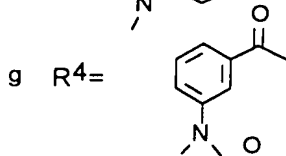
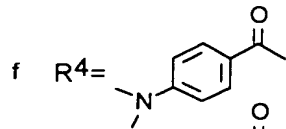
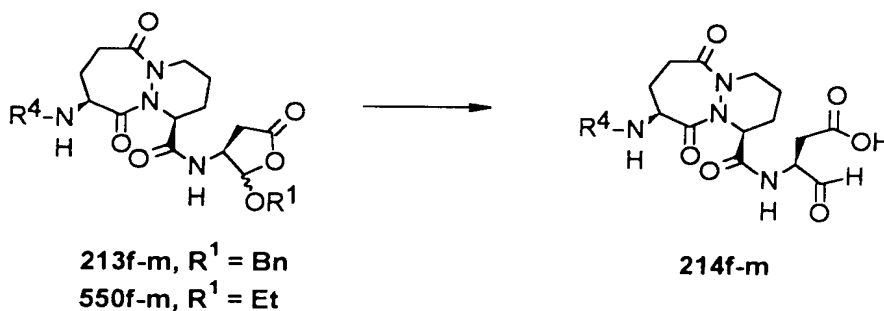
15 The hydrolysis may be carried out under various conditions, provided that the conditions include an acid and H₂O. Acids that may be used include p-toluensulfonic, methanesulfonic acid, sulfuric, perchloric, trifluoroacetic, and hydrochloric. For example, trifluoroacetic acid (1-90% by weight) or

- 551 -

hydrochloric acid (0.1-30% by weight) in CH₃CN/H₂O
(1-90% H₂O by weight) at between 0-50 °C may be used.

Example 29

Compounds 213f, 213g, 213h, 213i, 213j, 213k,
5 213l, 213m, 214f, 214g, 214h, 214i, 214j, 214k, 214l,
214m, 550f, 550g, 550h, 550i, 550j, 550k, 550l and 550m
were prepared as follows.



[1*S*,9*S*(2*RS*,3*S*)]9-[(4-Dimethylaminobenzoyl)amino]-6,10-
dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-Benzyloxy-5-
10 oxotetrahydrofuran-3-yl)-6H-
pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213f),
was synthesized from 212f by the methods used to

- 552 -

prepare **213e** from **212e** to afford 504 mg of **213f** as a yellow solid, ^1H NMR (CD_3OD) δ 1.10(br. m, 0.25H), 1.30(br. m, 2H), 1.50(br. m, 1H), 1.65(br. m, 1.5H), 1.80(br. m, 0.25H), 1.90(br. m, 0.25H), 1.95(br. m, 0.5H), 2.05(br. m, 0.25H), 2.15(m, 1H), 2.3(m, 1H), 2.5(br. m, 1H), 2.6(dd, 1H), 2.8(m, 1H), 3.1(br. s, 3H), 3.15(br. m, 1H), 3.32(br. s, 3H), 3.5(m, 1H), 4.5(br. m, 1H), 4.62(d, 0.25H), 4.72(m, 3H), 4.95(m, 1H), 5.1(br. t, 0.25H), 5.15(br. t, 0.75H), 5.7(d, 1H), 6.75(d, 2H), 7.35(br. s, 5H), 7.75(d, 2H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3-Dimethylaminobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (**213g**),
was synthesized from **212g** by the methods used to prepare **213e** from **212e** to afford 400 mg of **213g**, ^1H NMR (CD_3OD) δ 1.5(br. m, 1H), 1.65(br. m, 2H), 1.70(br. m, 0.25H), 1.90(br. m, 1H), 1.95(br. m, 1H), 2.05(br. m, 0.25H), 2.10(m, 1H), 2.3(m, 1H), 2.5(m, 2H), 2.59(d, 1H), 2.6(d, 1H), 2.78(d, 1H), 2.8(d, 1H), 2.93(br. s, 4H), 3.05(br. m, 1H), 3.15(br. m, 0.25H), 3.3(br. s, 3H), 3.5(m, 2H), 4.5(br. m, 2H), 4.65(d, 1H), 4.7(br. m, 2H), 4.95(br. m, 1H), 5.15(br. t, 0.25H), 5.2(br. t, 0.75H), 5.2(d, 1H), 6.95(d, 1H), 7.15(d, 1H), 7.25(br. s, 1H), 7.3(br. t, 2H), 7.45(br. s, 6H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3-Chloro-4-aminobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (**213h**),
was synthesized from **212h** by the methods used to

- 553 -

prepare **213e** from **212e** to afford 296 mg of **213h**, ^1H NMR (CDCl₃) δ 1.55-1.68(m, 1H), 1.7-2.05(m, 3H), 2.3-2.5(m, 2H), 2.65-2.8(m, 1H), 2.85-2.93(m, 1H), 2.95-3.25(m, 3H), 4.44-4.65(m, 2H), 4.68-4.82(m, 1H), 4.9-4.95(d, 1H), 5.05-5.18(m, 2H), 5.28(s, 0.5H), 5.55-5.58(d, 0.5H), 6.52-6.58(d, 0.5H), 6.7-6.76(m, 2H), 6.82-6.85(d, 0.5H), 7.3-7.4(m, 5H), 7.52-7.58(m, 1H), 7.75(s, 0.5H), 7.8(s, 0.5H).

[1S,9S(2RS,3S)]9-[(4-Methoxybenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213i), was synthesized from **212i** by the methods used to prepare **213e** from **212e** to afford 1.1 g of **213i**, ^1H NMR (CDCl₃) δ 1.55-2.05(m, 6H), 2.26-2.5(m, 2H), 2.68-2.82(m, 1H), 2.85-2.92(m, 1H), 2.95-3.25(m, 2H), 3.82(s, 1.5H), 3.85(s, 1.5H), 4.4-4.65(m, 2H), 4.7-4.78(m, 1H), 4.88-4.95(m, 1H), 5.05-5.23(m, 1H), 5.28(s, 0.5H), 5.55-5.58(d, 0.5H), 6.6-6.65(m, 1H), 6.8-6.84(m, 1H), 6.9-6.95(m, 3H), 7.3-7.45(m, 4H), 7.78-7.85(m, 2H).

[1S,9S(2RS,3S)]9-[(3,5-Dichlorobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213j), was synthesized from **212j** by the methods used to prepare **213e** from **212e** to afford 367 mg of **213j**, ^1H NMR (CDCl₃) δ 1.55-2.05(m, 12H), 2.25(d, 1H), 2.35(m, 1H), 2.48(m, 2H), 2.75(m, 2H), 2.9(m, 1H), 2.95-3.25(m, 5H), 4.45(t, 1H), 4.5-4.6(m, 4H), 4.7(m, 1H), 4.75(d, 1H),

- 554 -

4.88(m, 1H), 5.05(m, 2H), 5.15(q, 1H), 5.3(s, 1H),
5.58(d, 1H), 6.5(d, 1H), 6.9(d, 1H), 7.05(d, 1H), 7.25-
7.35(m, 5H), 7.6(s, 2H), 7.7(s, 2H).

- [1*S*,9*S*(2*RS*,3*S*)]9-[(3,5-Dichloro-4-
5 hydroxybenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-
octahydro-*N*-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6*H*-
pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide (213k),
was synthesized from 212k by the methods used to
prepare 213e from 212e to afford 593 mg of 213k, ¹H NMR
10 (CD₃OD) δ 1.5(m, 1H), 1.6-1.7(m, 2H), 1.75-1.95(m, 4H),
2.15(m, 2H), 2.3(m, 1H), 2.6(m, 1H), 2.7(m, 1H),
3.05(m, 2H), 3.15(m, 1H), 3.5(m, 2H), 4.45(m, 2H),
4.65(d, 1H), 4.7(m, 1H), 4.95(m, 1H), 5.15(m, 1H),
5.4(s, 1H), 5.7(d, 1H), 7.3(m, 5H), 7.85(s, 2H).
- 15 [1*S*,9*S*(2*RS*,3*S*)]9-[(3-Chloro-4-acetamidobenzoyl)amino]-
6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-*N*-(2-Benzyloxy-5-
oxotetrahydrofuran-3-yl)-6*H*-
pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide (213l),
was synthesized from 212l by the methods used to
20 prepare 213e from 212e to afford 133 mg of 213l, ¹H NMR
(CDCl₃) δ 1.55-1.7(m, 1H), 1.75-2.05(m, 3H), 2.25(s,
1.5H), 2.27(s, 1.5H), 2.3-2.48(m, 2H), 2.7-2.83(m, 1H),
2.85-2.94(dd, 1H), 2.95-3.25(m, 2H), 4.42-4.65(m, 2H),
4.68-4.85(m, 1H), 4.88-4.95(m, 1H), 5.05-5.18(m, 2H),
25 5.32(s, 0.5H), 5.55-5.6(d, 0.5H), 6.48-6.55(d, 1H),
6.88-6.92(d, 1H), 7.0-7.04(d, 0.5H), 7.15-7.2(d, 0.5H),
7.3-7.4(m, 4H), 7.64-7.78(m, 2H), 7.88-7.94(m, 1H),
8.45-8.56(m, 1H).

- [1*S*,9*S*(2*RS*,3*S*)]9-[(3,5-Dichloro-4-
30 methoxybenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-

- 555 -

- octahydro-N-(2-Benzylloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213m), was synthesized from 212m by the methods used to prepare 213e from 212e to afford 991 mg of 213m, ¹H NMR (CDCl₃) δ 1.5-2.15(m, 5H), 2.2-2.55(m, 3H), 2.6-3.3(m, 4H), 3.95(2s, 3H), 4.45-4.7(m, 2H), 4.7-4.85(m, 1H), 4.85-4.95(m, 1H), 5.05-5.25(m, 1H), 5.3(s, 0.5H), 5.6(d, 0.5H), 6.55(d, 0.5H), 6.85(d, 0.5H), 7.0(d, 0.5H), 7.25-7.6(m, 5.5H), 7.75(s, 1H), 7.85(s, 1H).
- 10 [1S,9S(2RS,3S)]9-[(4-Dimethylaminobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550f), was synthesized from 212f by the methods used to
- 15 prepare 213e from 212e to afford 420 mg of 550f as an off white solid, ¹H NMR (CDCl₃) δ 1.2-1.25(br. t, 3H), 1.35(m, 1H), 1.55(br. m, 1H), 1.88-2.02(br. m, 4H), 2.3(d, 1H), 2.35(m, 1H), 2.45(m, 1H), 2.55-2.75(m, 3H), 3.0(s, 6H), 3.25(m, 1H), 3.55(m, 1H), 3.65(m, 1H),
- 20 3.75(m, 1H), 3.9(m, 1H), 4.3(t, 1H), 4.55(m, 2H), 4.68(br. m, 1H), 3.9(m, 1H), 4.3(t, 1H), 4.55(m, 2H), 4.68(br. m, 1H), 4.95(br. m, 1H), 5.1(br. m, 2H), 5.45(d, 1H), 6.5(m, 2H), 7.7(m, 2H).

- [1S,9S(2RS,3S)]9-[(3-Chloro-4-aminobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550h), was synthesized from 212h by the methods used to prepare 213e from 212e to afford 195 mg of 550h as a
- 30 white solid, ¹H NMR (DMSO-d₆) δ 1.1-1.18(2t, 3H), 1.6-

- 556 -

1.7(m, 2H), 1.88-2.05(m, 2H), 2.1-2.35(m, 3H), 2.48-
2.56(m, 1H), 2.75-2.8(m, 0.75H), 2.88-3.08(m, 1.25H),
3.25-3.4(m, 1H), 3.55-3.8(m, 2H), 4.35-4.45(m, 1H),
4.55-4.62(m, 1H), 4.8-4.88(m, 1H), 4.98-5.03(m, 0.25H),
5 5.1-5.13(m, 0.75H), 5.33(s, 0.25H), 5.58-5.6(d, 0.75H),
5.9-6.0(br. s, 2H), 6.8-6.85(d, 1H), 7.58-7.62(d, 1H),
7.82(s, 1H), 8.22-8.28(d, 1H), 8.48-8.52(d, 0.75H),
8.72-8.76(d, 0.25H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(4-Methoxybenzoyl)amino]-6,10-dioxo-
10 1,2,3,4,7,8,9,10-octahydro-N-(2-ethoxy-5-
oxotetrahydrofuran-3-yl)-6H-
pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550i),
was synthesized from 212i by the methods used to
prepare 213e from 212e to afford 135 mg of 550i, ¹H NMR
15 (CDCl₃) δ 1.18-1.28(2t, 3H), 1.6-1.75(m, 1.5H), 1.9-
2.1(m, 3.5H), 2.22-2.3(d, 0.5H), 2.38-2.47(m, 1.5H),
2.7-2.8(m, 0.5H), 2.8-2.93(m, 1H), 2.94-3.15(m, 1.5H),
3.15-3.28(m, 1H), 3.55-3.62(q, 0.5H), 3.62-3.73(q,
0.5H), 3.78-3.88(q, 0.5H), 3.88(s, 3H), 3.9-3.95(q,
20 0.5H), 4.33-4.4(m, 0.5H), 4.5-4.55(m, 1H), 4.68-4.76(m,
0.5H), 4.9-4.95(m, 0.5H), 5.1-5.2(m, 1.5H), 5.18(s,
0.5H), 5.48-5.52(d, 0.5H), 6.48-6.55(d, 0.5H), 6.85-
6.9(m, 1H), 6.9-6.95(m, 2H), 7.34-7.38(d, 0.5H), 7.78-
7.85(m, 2H).

25 [1*S*,9*S*(2*RS*,3*S*)]9-[(3,5-Dichloro-4-
hydroxybenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-
octahydro-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-6H-
pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550k),
was synthesized from 212k by the methods used to
30 prepare 213e from 212e to afford 174 mg of 550k as a
white solid, ¹H NMR (DMSO-d₆) δ 1.15(2t, 3H), 1.6-

- 557 -

1.75(m, 2H), 1.9-2.05(m, 2H), 2.1-2.4(m, 5H), 2.5-
 2.55(m, 1H), 2.7-2.8(m, 0.5H), 2.85-3.0(m, 1H), 3.0-
 3.1(m, 0.5H), 3.55-3.7(m, 1H), 3.7-3.8(m, 1H), 4.2(t,
 0.5H), 4.35-4.45(m, 0.5H), 4.55-4.65(m, 0.5H), 4.8-
 5 4.9(m, 0.5H), 5.05(t, 0.5H), 5.15(t, 0.5H), 5.35(s,
 0.5H), 5.6(d, 0.5H), 7.95(s, 2H), 8.5(d, 0.5H), 8.65(d,
 1H), 8.75(d, 0.5H), 10.9(br. s, 1H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3-Chloro-4-acetamidobenzoyl)amino]-
 6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-*N*-(2-ethoxy-5-
 10 oxotetrahydrofuran-3-yl)-6H-
 pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide (5501),
 was synthesized from 2121 by the methods used to
 prepare 213e from 212e to afford 151 mg of 5501, ¹H NMR
 (CDCl₃) δ 1.2-1.28(2t, 3H), 1.6-1.72(m, 1.5H), 1.88-
 15 2.15(m, 3.5H), 2.22-2.28(m, 0.5H), 2.28(s, 3H), 2.38-
 2.48(m, 1.5H), 2.66-2.92(m, 1.5H), 2.95-3.14(m, 1.5H),
 3.2-3.34(m, 1H), 3.56-3.63(q, 0.5H), 3.63-3.72(q,
 0.5H), 3.8-3.85(q, 0.5H), 3.9-3.95(q, 0.5H), 4.32-
 4.38(m, 0.5H), 4.5-4.62(m, 1H), 4.68-4.75(m, 0.5H),
 20 4.88-4.92(m, 0.5H), 5.08-5.2(m, 1.5H), 5.18(s, 0.5H),
 5.46-5.5(d, 0.5H), 6.5-6.55(d, 0.5H), 6.98-7.05(m, 1H),
 7.42-7.48(d, 0.5H), 7.63-7.78(m, 2.5H), 7.9-7.94(d,
 0.5H), 8.44-8.52(m, 1H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3,5-Dichloro-4-
 25 methoxybenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-
 octahydro-*N*-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-6H-
 pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide (550m),
 was synthesized from 212m by the methods used to
 prepare 213e from 212e to afford 301 mg of 550m as a
 30 white solid, ¹H NMR (CDCl₃) δ 1.2-1.35(2t, 3H), 1.5-

- 558 -

1.8(m, 2H), 1.9-2.15(5H), 2.25(d, 0.5H), 2.4-2.5(m, 2H), 2.65-2.8(m, 0.5H), 2.8-3.0(m, 0.5H), 3.0-3.2(m, 1H), 3.2-3.35(m, 0.5H), 3.55-3.65(m, 0.5H), 3.65-3.75(m, 0.5H), 3.8-3.9(m, 0.5H), 3.9-4.0(m, 0.5H), 4.4-4.45(m, 0.5H), 4.55-4.65(m, 0.5H), 4.7-4.8(m, 0.5H), 4.85-4.95(m, 0.5H), 5.05-5.2(m, 0.5H), 5.2(s, 0.5H), 5.5(d, 0.5H), 6.5(d, 0.5H), 6.9(d, 0.5H), 6.95(d, 0.5H), 7.35(d, 0.5H), 7.75(s, 1H), 7.85(s, 1H).

[3S(1S,9S)]3-(9-(3,5-Dichlorobenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (214j), was synthesized from 213j by the method used to prepare 2002 from 2001 to afford 62 mg of 214j as a white solid, ¹H NMR (CD₃OD) δ 0.9 (t, 1H), 1.3(br. s, 1H), 1.7(br. m, 1H), 1.9(br. m, 1H), 2.1(br. s, 1H), 2.25(q, 1H), 2.35(m, 1H), 2.48(m, 2H), 2.65(t, 1H), 3.15(br. t, 1H), 3.5(br. m, 1H), 4.3(br. s, 1H), 4.55(m, 2H), 4.95(t, 1H), 5.25(br. s, 1H), 7.6(br. s, 1H), 7.85(br. s, 1H).

[3S(1S,9S)]3-(9-(3,5-Dichloro-4-hydroxybenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (214k), was synthesized from 213k by the method used to prepare 2002 from 2001 to afford 80 mg of 214k as a white solid, ¹H NMR (CD₃OD) δ 1.6-1.7(m, 1H), 1.8-2.0(m, 2H), 2.0-2.1(m, 2H), 2.15-2.25(m, 1H), 2.3-2.4(m, 1H), 2.4-2.55(m, 2H), 2.6-2.75(m, 1H), 3.05-3.2(m, 1H), 3.4-3.6(m, 2H), 4.2-4.3(m, 1H), 4.45-4.6(m, 1H), 4.8-5.0(m, 1H), 5.1-5.2(m, 1H), 7.85(s, 2H).

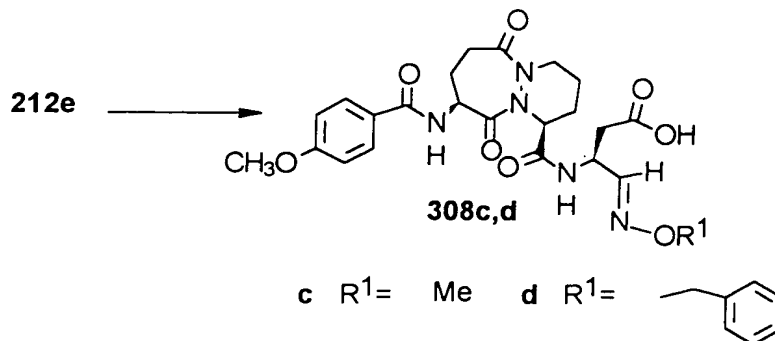
- 559 -

[3*S*(1*S*,9*S*)]3-(9-(3-Chloro-4-acetamidobenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (**2141**), was synthesized from **2131** by the method used to prepare **2002** from **2001** to afford 91 mg of **2141** as a white solid, ¹H NMR (DMSO-*d*₆) δ 1.65(br. m, 6H), 1.9(br. m, 6H), 2.15(s, 3H), 2.3(m, 3H), 2.6-2.85(m, 3H), 2.9(m, 2H), 3.0(m, 1H), 4.15(br. q, 1H), 4.4(m, 3H), 5.0(m, 1H), 5.15(m, 1H), 5.45(s, 1H), 7.8(d, 2H), 7.95(d, 1H), 8.05(s, 1H), 8.65(m, 2H), 9.65(s, 1H).

[3*S*(1*S*,9*S*)]3-(9-(3,5-Dichlorobenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (**214m**), was synthesized from **213m** by the method used to prepare **2002** from **2001** to afford 105 mg of **214m** as a white solid, ¹H NMR (CD₃OD) δ 1.6-1.75(m, 1H), 1.85-1.95(m, 1H), 2.0-2.1(m, 2H), 2.15-2.25(m, 1H), 2.3-2.4(m, 1H), 2.45-2.55(m, 2H), 2.65-2.75(m, 1H), 3.4-3.55(m, 2H), 3.95(s, 3H), 4.2-4.3(m, 1H), 4.45-4.6(m, 1H), 4.9-5.0(m, 1H), 5.15-5.2(m, 1H), 7.9(s, 2H).

Compounds **308c** and **308d** were prepared as follows.

- 560 -



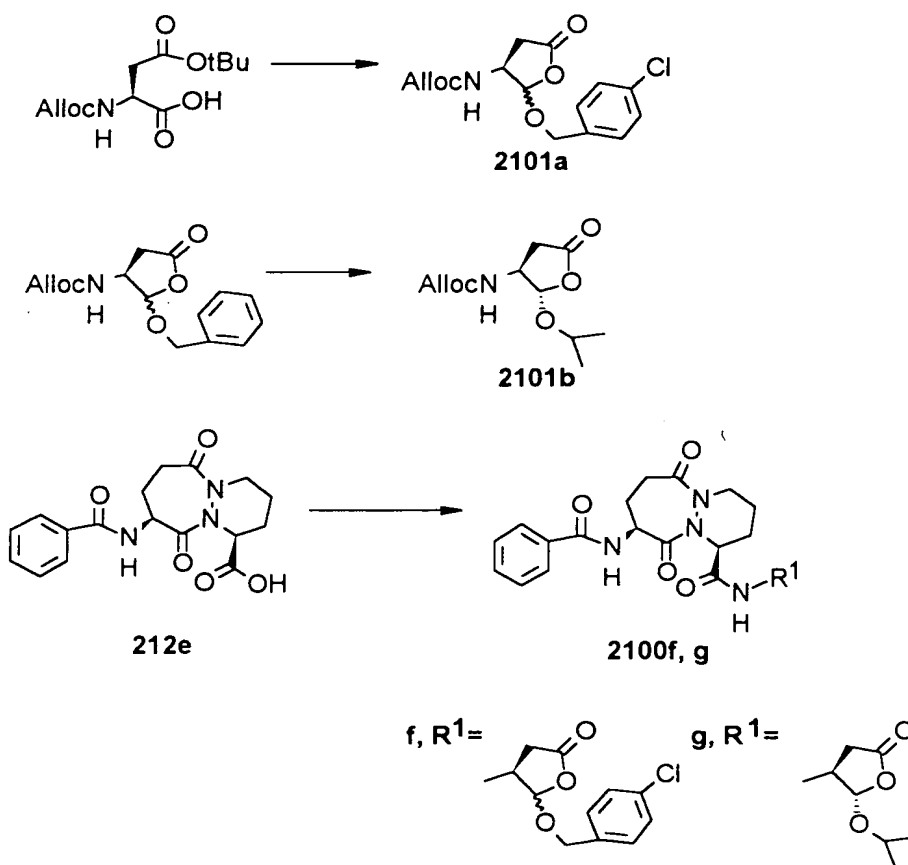
[3*S*(1*S*,9*S*) 3-(9-(4-Methoxybenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-amino]-4-oxobutanoic acid, O-methyl oxime (308c), was
 5 synthesized from 212e via the methods used to prepare 308b from 212e to afford 266 mg of 308c ¹H NMR (CDCl₃) δ 1.6-1.7(m, 1H), 1.88-1.98(m, 3H), 2.02-2.15(m, 1H), 2.3-2.4(m, 1H), 2.65-2.95(m, 3H), 3.04-3.09(m, 1H), 3.12-3.25(m, 1H), 3.84(s, 3H), 3.86(s, 3H), 4.5-4.58(m,
 10 1H), 4.88-4.95(m, 1H), 5.1-5.25(m, 2H), 6.86-6.9(d, 2H), 7.15-7.25(m, 2H), 7.36-7.4(m, 1H), 7.75-7.8(d, 2H).

[3*S*(1*S*,9*S*) 3-(9-(4-Methoxybenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-amino]-4-oxobutanoic acid, O-benzyl oxime (308d), was
 15 synthesized from 212e via the methods used to prepare 308b from 212e to afford 270 mg of 308d, ¹H NMR (CDCl₃) δ 1.55-1.65(m, 1H), 1.8-2.1(m, 4H), 2.3-2.4(m, 1H), 2.65-2.88(m, 3H), 2.9-3.3(m, 3H), 4.5-4.58(m, 1H),
 20 4.88-4.95(m, 1H), 5.05(s, 2H), 5.1-5.2(m, 1H), 6.82-

- 561 -

6.95(m, 2H), 7.02-7.15(m, 2H), 7.28(m, 5H), 7.45(m, 1H), 7.72(d, 2H).

Compounds **2100f**, **2100g**, **2100h**, **2100i** and **2100j** were prepared as described below.



5 (3*S*,2*RS*) 3-Allyloxycarbonylamino-2-(4-chlorobenzyl)oxy-5-oxotetrahydrofuran (**2101a**), was synthesized from allyloxycarbonylamino-β-tert-butyl aspartate by the methods employed by Chapman (Bioorg. & Med. Chem. Lett., 2, pp.615-618 (1992)) to prepare (3*S*,2*RS*) 3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran

10

- 562 -

using 4-chlorobenzyl alcohol instead of benzyl alcohol to afford 1.84 g of **2101a** as a crystalline solid.

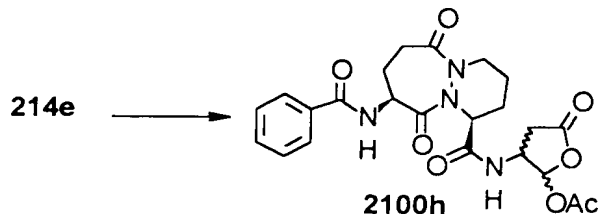
[1S,9S(2RS,3S)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-(4-chlorobenzyl)oxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100f), was synthesized from **212e** by the methods used to prepare **213e** from **212e** using **2101a** to afford 380 mg of **2100f**, ¹H NMR (CDCl₃) δ 1.8-2.0(m, 10H), 2.30(d, 1H), 2.31-2.5(m, 3H), 2.7-2.9(m, 3H), 3.05(m, 2H), 3.1-3.2(m, 4H), 4.45(q, 1H), 4.5-4.6(m, 3H), 4.7(d, 2H), 4.85(d, 1H), 4.9(t, 1H), 5.2(t, 1H), 5.15(m, 2H), 5.25(s, 1H), 5.55(d, 1H), 6.5(d, 1H), 6.9(d, 1H), 6.95(d, 1H), 7.25(m, 3H), 7.35(t, 2H), 7.45(m, 2H), 7.55(1H), 7.8(m, 3H).

(3S,2RS) 3-Allyloxycarbonylamino-2-anti-isopropoxy-5-oxotetrahydrofuran (2101b), was synthesized from **(3S,2RS) 3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran** via the method used to prepare **2100d** from **214e** using H₂SO₄ instead of pTSA to afford **2101b**.

[1S,9S(2RS,3S)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-anti-isopropoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100g), was synthesized from **212e** by the methods used to prepare **213e** from **212e** using **2101b** to afford 31 mg of **2100g**, ¹H NMR (CDCl₃) δ 1.19 (d), 1.94 (br s), 2.00-2.12 (m), 2.24 (d), 2.42 (dd), 2.71-2.83 (m), 3.02 (dd), 3.12-3.27 (overlapping m), 3.93 (m), 4.32-4.37 (m),

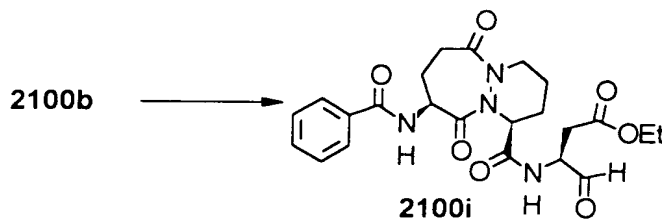
- 563 -

4.52-4.63 (m), 4.90-4.95 (m), 5.12-5.20 (m), 5.28 (s),
6.93 (d), 7.10 (d), 7.41-7.50 (m), 7.51-7.58 (m), 7.84
(d).



[1*S*,9*S*(2*RS*,3*RS*)] 9-Benzoylamino-6,10-dioxo-
5 1,2,3,4,7,8,9,10-octahydro-N-(2-acetoxy-5-
oxotetrahydrofuran-3-yl)-6H-
pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100h).
A solution of **214e** (287 mg, 0.65 mmol) in pyridine (5
mL) was treated with Ac₂O (0.4 mL, 3.62 mmol). After 6
10 hours, the reaction mixture was poured into 5% NaHSO₄
and extracted 3 times with EtOAc. The combined
organics were washed with brine, dried over Na₂SO₄ and
concentrated *in vacuo*. Chromatography (SiO₂, EtOAc)
afforded 119 mg of **2100h**, ¹HNMR (CDCl₃, mixture of four
15 diastereoisomers) δ 1.80-2.05(m), 2.12(s), 2.13(s),
2.19(s), 2.22(d), 2.67-2.75(m), 2.80-2.95(m), 3.00-
3.20(m), 3.21-3.33(m), 3.50-3.95(four discrete
multiplets), 4.19(m), 4.55(m), 4.57-4.65(m), 4.69(m),
4.85-4.95(m), 5.04(m), 5.10(s), 5.10-5.22(m), 6.46(d),
20 6.03(s), 6.50(d), 6.58(d), 6.75(d), 6.95-7.05(m),
7.22(m), 7.30(m), 7.71(d), 7.75-7.83(m).

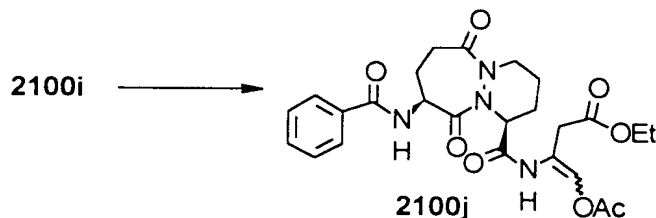
- 564 -



[3*S*(1*S*,9*S*)]3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid ethyl ester (2100i). To a solution of

5 2100b (1.5 g, 2.7 mmol) in CH₃CN (10 mL) was added 1*N* HCl at ambient temperature. After 6 hours solid NaHCO₃ was added and the product extracted with EtOAc, dried over MgSO₄ and concentrated *in vacuo*. Chromatography (SiO₂, 30-100% CH₂Cl₂ in EtOAc) afforded 123 mg of

10 2100i, ¹H NMR (CDCl₃) δ 1.25(t, 3H), 1.6-1.8(m, 1H), 1.9-2.2(m, 5H), 2.4-2.5(m, 1H), 2.75-2.9(m, 2H), 3.0-3.1(m, 2H), 3.2-3.25(m, 1H), 4.05-4.2(m, 1H), 4.5-4.7(m, 1H), 5.1-5.25(m, 1H), 7.0-7.2(m, 2H), 7.4-7.45(m, 2H), 7.5(t, 1H), 7.8(t, 2H), 9.5(s, 1H).



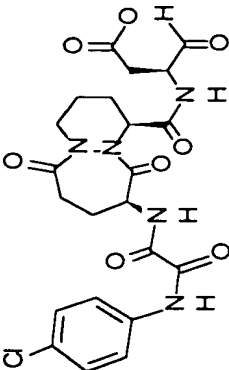
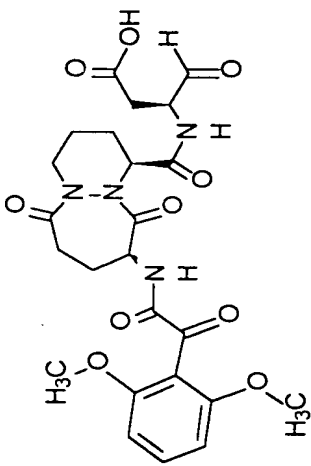
15 [3*S*(1*S*,9*S*)]3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-4-acetoxy-3-butenic acid ethyl ester (2100j), was synthesized from 2100i via the method used to prepare

- 565 -

2100h from 214e to afford 347 mg of 2100j, ¹H NMR
(CDCl₃) δ 1.3(t, 3H), 1.6-1.8(m, 2H), 1.9-2.25(m, 4H),
2.25(s, 3H), 2.3-2.45(m, 1H), 2.8-3.0(m, 1H), 3.0-
3.25(m, 2H), 3.4-3.45(m, 2H), 4.1-4.2(m, 2H), 4.55-
5 4.7(m, 1H), 5.1-5.25(m, 1H), 6.8(s, 1H), 7.0-7.1(m,
2H), 7.5(t, 1H), 7.8(t, 2H), 9.5(s, 1H).

Compounds 500 and 501 are described in Table
23. These compounds were prepared by methods similar
to the methods used to prepare compounds 404-449 (see,
10 Example 11).

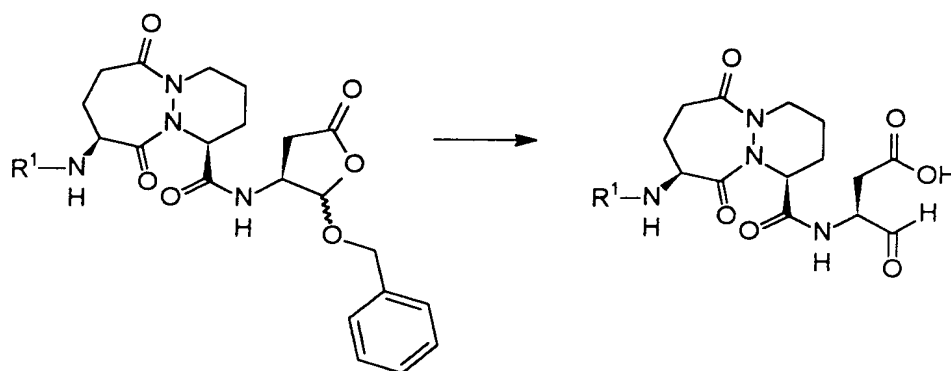
Table 23

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+H) +
500		C22H24ClN5O8	521.92	11.448 (A) 0.991	523.1
501		C24H28N4O10	532.51	10.13 0.97	533

- 567 -

The compounds described below (213m, 213n, 213o, 213p, 213q, 213r, 213s, 213t, 213u, 213v, 213w, 213x, and 214w), were prepared by methods similar to the methods used to prepare compounds 213b-f.

5 Compounds 419, 415, 450, 456, 475, 404, 486, 487, 417, 408 and 418 may also be prepared as described below.



213m-x
214w, 404, 408, 415,

10

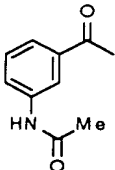
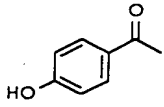
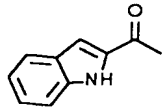
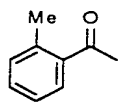
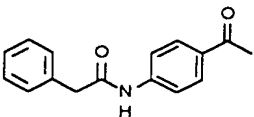
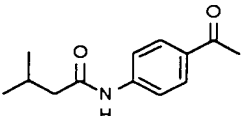
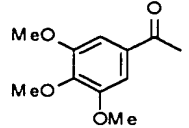
417, 418, 419, 450,

15

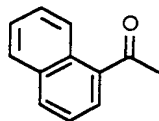
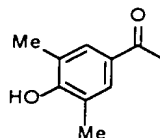
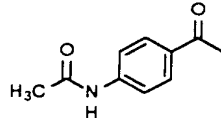
456, 475, 486, 487

compound	R ¹
213m, 419	MeOC(O) -
213n, 415	

- 568 -

213o, 450	
213p, 456	
213q, 475	
213r, 404	
213s, 486	
213t, 487	
213u, 417	

- 569 -

213v, 408	
213w, 214w	
213x, 418	

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzoyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213n), was isolated as a mixture of diastereomers (syn:anti isomer ratio 6:4) (1.43g, 82%) as a white solid: mp. 206-10°C; IR (KBr) 3288, 1787, 1680, 1657, 1651, 1619, 1548, 1440, 1256, 1135; ¹H NMR (D₆-DMSO) δ 8.75 (0.4H, d), 8.55 (0.6H, d), 8.45 and 8.43 (1H, 2 x d), 7.50 (1H, d), 7.42 (1H, s), 7.40-7.27 (5H, m), 7.01 (1H, d), 6.11 (2H, s), 5.67 (0.6H, d), 5.43 (0.4H, s), 5.10-5.00 (1H, m), 4.90-4.59 (3.5H, m), 4.45-4.25 (1.5H, m), 3.47-3.20 (1H, m), 3.20-2.70 (2H, m), 2.65-2.35 (1H, m), 2.35-2.00 (3H, m), 2.00-1.75 (2H, m), 1.65-1.40 (2H, m). Anal. Calcd for C₂₉H₃₀N₄O₉: C, 60.20; H, 5.23; N, 9.68. Found: C, 60.08; H, 5.32; N, 9.50. MS (ES⁺)

- 570 -

580 ($M^+ + 2$, 35%), 579 ($M^+ + 1$, 100), 404 (5), 367 (5),
236 (7), 107 (5).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3-Acetamido)benzamido]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-
5 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213o),
anti-isomer as a white foamy solid (0.73g, 69%): mp. 135-40°C; $[\alpha]_D^{21}$ -37.3° (c 0.1, CH₂Cl₂); IR (KBr) 3452, 3310, 1790, 1664, 1659, 1650, 1549, 1425, 1258, 1121;
10 ¹H NMR (D₆-DMSO) δ 10.11 (1H, s), 8.77 (1H, d), 8.57 (1H, d), 8.01 (1H, s), 7.76 (1H, d), 7.55 (1H, d), 7.45-7.25 (6H, m), 5.43 (1H, s), 5.08-5.00 (1H, m), 4.95-4.73 (1H, m), 4.76 and 4.68 (2H, dd), 3.40-3.20 (1H, m), 3.09 (1H, dd), 3.02-2.75 (1H, m), 2.45-2.06
15 (4H, m), 2.06 (3H, s), 2.00-1.75 (2H, m), 1.70-1.40 (2H, m). Anal. Calcd for C₃₀H₃₃N₅O₈•0.75H₂O: C, 59.54; H, 5.75; N, 11.57. Found: C, 59.40; H, 5.62; N, 11.50. MS (ES⁺) 593 ($M^+ + 2$, 33%), 592 ($M^+ + 1$, 100), 574 (7), 487 (7), 475 (6), 385 (9), 373 (26), 318 (14), 296
20 (11), 266 (10), 221 (22).

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(4-hydroxybenzoyl)amino-
1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213p),
25 was isolated as a foam (1.2g, 77%): $[\alpha]_D^{20}$ -115° (c 0.20, CH₂Cl₂); IR (KBr) 3368, 2946, 1794, 1654, 1609, 1540, 1505, 1421, 1277, 1175, 1119, 980; ¹H NMR (D₆-DMSO) δ 10.1 (1H, s), 8.80 (0.5H, d, J = 6.6), 8.60 (0.5H, d, J = 7.2), 8.40-8.36 (1H, 2d), 7.82 (2H, d, J = 8.0), 7.41 (5H, bs), 6.86 (2H, d, J 8.6), 5.72 (0.5H,
30 = 8.0), 5.72 (0.5H, bs), 5.43 (1H, s), 5.08-5.00 (1H, m), 4.95-4.73 (1H, m), 4.76 and 4.68 (2H, dd), 3.40-3.20 (1H, m), 3.09 (1H, dd), 3.02-2.75 (1H, m), 2.45-2.06 (4H, m), 2.06 (3H, s), 2.00-1.75 (2H, m), 1.70-1.40 (2H, m).

- 571 -

d, $J = 5.0$), 5.49 (0.5H, bs), 5.13-5.07 (1H, m), 4.95-4.65 (2.5H, m), 4.49-4.38 (2.5H, m), 3.49-3.30 (2H, m), 3.21, 2.79 (2H, m), 2.40-1.41 (7H, m). MS (ES^+) 551.

[1*S*,9*S*(2*RS*,3*S*)]N-(2-Benzylloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(indol-2-oylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213q), was isolated as a white glassy solid (80%): mp. 145-149°C; $[\alpha]_D^{23} -56.0^\circ$ (c 0.05, CH_2Cl_2); IR (KBr) 3399-3319, 1791, 1657, 1543, 1420, 1253, 1119; 1H NMR ($CDCl_3$) δ 9.54 (1H, s), 7.65 (1H, d, $J = 7.9$), 7.51 (1H, d, $J = 6.9$), 7.44-7.25 (7H, m), 7.18-7.06 (3H, m), 5.30-5.20 (1H, m), 5.27 (1H, s), 4.84 (1H, m), 4.79 (1H, d, $J = 11.4$), 4.56 (1H, d, $J = 11.3$), 4.47 (2H, m), 3.28 (1H, m), 3.10-2.97 (2H, m), 2.71 (1H, m), 2.47-2.37 (1H, m), 2.26 (1H, d, $J = 17.9$), 2.09 (1H, m), 1.83, 1.70, 1.51 (4H, 3m).

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzylloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-9-(2-toluoylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213r), was isolated as a mixture of diastereomers (syn:anti isomer ratio 55:45) as a white foamy solid (1.46g, 89%): mp. 106-10°C; IR (KBr) 3306, 2947, 1791, 1659, 1650, 1535, 1421, 1256, 1122; 1H NMR (D_6 -DMSO) δ 8.76 (0.45H, d), 8.56 (0.55H, d), 8.49 and 8.47 (1H, 2 x d), 7.41-7.19 (9H, m), 5.67 (0.55H, d), 5.43 (0.45H, s), 5.11-5.02 (1H, m), 4.86-4.55 (3.5H, m), 4.45-4.25 (1.5H, m), 3.40-3.20 (1H, m), 3.20-2.70 (2H, m), 2.65-2.40 (1H, m), 2.34 (3H, s), 2.30-1.70 (5H, m), 1.65-1.40 (2H, m). Anal. Calcd for $C_{29}H_{32}N_4O_7$: C, 62.66; H, 5.95; N, 10.08. Found: C, 62.91; H, 6.00;

- 572 -

N, 9.70. MS (ES^+) 550 ($\text{M}^+ + 2$, 43%), 549 ($\text{M}^+ + 1$, 100), 374 (3), 280 (4), 279 (20), 118 (5).

[1*S*,9*S*(2*RS*,3*S*)]N-(2-Benzylloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-9-[4-(phenylacetamido)benzamido]-6H-pyridazino[1,2-a][1,2]diazepin-1-carboxamide (213s),
 5 was isolated as the anti-isomer as a white foamy solid (0.64g, 77%): mp. 137-41°C; $[\alpha]_{\text{D}}^{21}$ -48.2° (c 0.05, CH_3OH); IR (KBr) 3477, 3314, 1791, 1659, 1599, 1529,
 10 1499, 1406, 1256, 1122; ^1H NMR (D_6 -DMSO) δ 10.45 (1H, s), 8.76 (1H, d), 8.50 (1H, d), 7.86 (2H, d), 7.69 (2H, d), 7.41-7.20 (10H, m), 5.43 (1H, s), 5.08-4.98 (1H, m), 4.90-4.73 (1H, m), 4.76 and 4.68 (2H, dd), 3.67 (2H, s), 3.40-3.20 (1H, m), 3.09 (1H, dd), 3.02-2.75
 15 (1H, m), 2.39 (1H, dd), 2.30-2.00 (3H, m), 2.00-1.75 (2H, m), 1.70-1.40 (2H, m). Anal. Calcd for $\text{C}_{36}\text{H}_{37}\text{N}_5\text{O}_8 \cdot 0.5\text{H}_2\text{O}$: C, 63.90; H, 5.66; N, 10.35. Found: C, 63.68; H, 5.67; N, 10.24. MS (ES^+) 669 ($\text{M}^+ + 2$, 40%), 668 ($\text{M}^+ + 1$, 100), 640 (12), 435 (18), 425 (23),
 20 403 (33), 328 (17), 302, (32), 274 (22), 197 (16), 138 (17).

[1*S*,9*S*(2*RS*,3*S*)]N-(2-Benzylloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-[4-(3-methylbutan-1-oylamino)benzamido]-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213t),
 25 was isolated as a white foamy solid (0.63g, 80%): mp. 159-64°C; $[\alpha]_{\text{D}}^{21}$ -37.0° (c 0.05, CH_3OH); IR (KBr) 3463, 3321, 1790, 1680, 1658, 1650, 1644, 1595, 1525, 1501, 1408, 1251, 1113, 933; ^1H NMR (D_6 -DMSO) δ 10.13 (1H, s),
 30 8.76 (1H, d), 8.48 (1H, d), 7.85 (2H, d), 7.68 (2H, d),

- 573 -

7.40-7.25 (5H, m), 5.43 (1H, s), 5.08-4.95 (1H, m),
 4.92-4.73 (1H, m), 4.76 and 4.68 (2H, dd), 3.40-3.20
 (1H, m), 3.09 (1H, dd), 3.02-2.75 (1H, m), 2.39 (1H,
 dd), 2.35-2.00 (6H, m), 2.00-1.75 (2H, m), 1.70-1.40
 5 (2H, m), 0.93 (6H, d). Anal. Calcd for
 $C_{33}H_{39}N_5O_8 \cdot 0.5H_2O$: C, 61.67; H, 6.27; N, 10.90. Found:
 C, 61.49; H, 6.24; N, 10.86. MS (ES^+) 635 ($M^+ + 2$,
 39%), 634 ($M^+ + 1$, 100), 484 (10), 427 (9), 274 (18),
 268 (37), 204 (19), 117 (13).

10 **[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzylloxy-5-oxotetrahydrofuran-3-
 yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-9-(3,4,5-
 trimethoxybenzoylamino)-6H-
 pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213u),
 was isolated as a white solid (81%): mp. 120-132°C; IR
 15 (KBr) 3361-3334, 1792, 1659, 1585, 1536, 1499, 1457,
 1416, 1340, 1236, 1126, 989; 1H NMR ($CDCl_3$) δ 7.39-7.29
 (6H, m), 7.12 (1H, s), 7.03 (1H, s), 6.92, 6.83, 6.48
 (approx 3H, 3d, $J = 8.1, 7.5, 8.1$), 5.57 (d, $J = 5.3$),
 5.27 (1H, s), 5.23-5.06, 4.91-4.71, 4.64-4.43, (6H,
 20 3m), 3.92, 3.91, 3.89, 3.88 (9H, 4s), 3.32-2.70, 2.52-
 2.08, 1.91, 1.63 (1H, 4m).**

**[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzylloxy-5-oxotetrahydrofuran-3-
 yl)-6,10-dioxo-9-(naphth-1-oylamino)-1,2,3,4,7,8,9,10-
 octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-
 25 carboxamide (213v), was isolated as a white solid
 (78%): mp. 121-7°C; IR (KBr) 3534-3331, 1791, 1659,
 1528, 1420, 1256, 1122; 1H NMR ($CDCl_3$) δ 8.34-8.29 (1H,
 m), 7.98-7.87 (2H, m), 7.68-7.45 (4H, m), 7.34-7.24
 (5H, m), 7.04 (d, $J = 6.8$), 6.78 (d, $J = 7.8$), 6.66 (d,
 30 $J = 7.7$), 6.48 (2H, d, $J = 7.5$) 5.56 (d, $J = 5.4$), 5.15**

- 574 -

(1H, s), 5.30-5.14, 5.0, 4.89 (d, $J = 11.2$), 4.71-4.41 (6H), 3.18-2.80, 2.50-2.27, 2.08-1.60 (11H, 3m).

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzylloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(4-hydroxy-3,5-dimethylbenzoyl)amino-
 5 **1,2,3,4,7,8,9,10-octahydro-6H-**
pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213w),
 was isolated as a mixture of diastereoisomers (65/35) as a white solid (0.9g, 65%): mp. 110-115°C (decomp.); IR (KBr) 3409, 2945, 1792, 1658, 1606, 1534, 1486,
 10 1420, 1330, 1276, 1209, 1122, 980, 960; ^1H NMR (CDCl_3) δ 7.66 (0.35H, d, $J = 6.9$), 7.46-7.20 (7H, m), 6.93 (0.35H, d, $J = 7.7$), 6.85 (0.65H, d, $J = 7.6$), 6.73 (0.65H, d, $J = 7.6$), 5.96 (0.35H, bs), 5.85 (0.65H, bs), 5.56 (0.65H, d, $J = 5.2$), 5.28 (0.35H, bs), 5.20-
 15 4.98 (2H, m), 4.96-4.40 (4H, m), 3.28-2.55 (3H, m), 2.53-2.32 (1H, m), 2.23 (6H, 2s), 2.03-1.40 (7H, m). MS (ES^-) 577, (ES^+) 579.

[1*S*,9*S*(2*RS*,3*S*)] 9-[4-(Acetylamino)benzoylamino]-N-(2-benzylloxy-5-oxo-tetrahydrofuran-3-yl)-6,10-dioxo-
 20 **1,2,3,4,7,8,9,10-octahydro-6H-**
pyridazino[1,2-a][1,2]diazepine-1-carboximide (213x),
 was isolated as a colourless powder (691mg, 86%): mp. 150-70°C; $[\alpha]_D^{22} -10.1^\circ$ (c 0.10, Me_2CO); IR (KBr) 3313, 1791, 1679, 1654, 1597, 1528, 1501, 1457, 1407, 1371,
 25 1315, 1255, 1184, 1122, 933; ^1H NMR ($\text{d}_6\text{-DMSO}$) δ 8.75 (1H, d), 8.47 (1H, d), 7.84 (2H, d), 7.66 (2H, d), 7.35 (5H, m), 5.43 (1H, s), 5.06-5.00 (1H, m), 4.90-4.64 (3H, m), 4.46-4.26 (2H, m), 3.16-2.86 (2H, m), 2.45-2.05 (5H, m), 2.07 (3H, s), 2.00-1.84 (2H, m), 1.68-1.56 (2H, m);
 30 Anal. Calcd for $\text{C}_{30}\text{H}_{33}\text{N}_5\text{O}_8 \cdot \text{H}_2\text{O}$: C, 59.11; H, 5.79; N,

- 575 -

11.49. Found: C, 59.38; H, 5.66; N, 11.31; M.S. (ES^+) 614 (100%), 592 ($\text{M}^+ + 1.66$).

[3S(1S,9S)] 3-[6,10-Dioxo-9-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-
 5 6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (415), was prepared by a similar method as compound 214e to afford a white solid (297mg, 84%): mp. 158-62°C; $[\alpha]_{\text{D}}^{24} -109.5^\circ$ (c 0.1, CH_3OH); IR (KBr) 3700-2500 (br), 1783, 1659, 1650, 1538, 1486,
 10 1439, 1257, 1037; ^1H NMR (CD_3OD) δ 7.48 (1H, dd), 7.35 (1H, d), 6.88 (1H, d), 6.03 (2H, s), 5.25-5.15 (1H, m), 5.02-4.90 (1H, m), 4.63-4.45 (2H, m), 4.30-4.20 (1H, m), 3.57-3.30 (1H, m), 3.20-3.05 (1H, m), 2.75-2.10 (5H, m), 2.10-1.60 (4H, m). MS (ES^+) 488 (M^+ , 25%),
 15 487 ($\text{M}^+ - 1$, 100), 443 (8), 387 (3), 315 (5), 150 (6), 127 (5), 113 (8). Accurate mass calculated for $\text{C}_{22}\text{H}_{25}\text{N}_4\text{O}_9$ (MH^+): 489.1621. Found 489.1648.

[3S(1S,9S)] 3-{9-[(3-Acetamido)benzamido]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-
 20 pyridazino[1,2-a][1,2]diazepine-1-carboxamido}-4-oxobutanoic acid (450), was prepared by a similar method as compound 214e to afford a white foamy solid (378mg, 94%): mp. 175-9°C; $[\alpha]_{\text{D}}^{22} -91.7^\circ$ (c 0.1, CH_3OH); IR (KBr) 3700-2500 (br), 3319, 1659, 1590, 1553, 1427,
 25 1260; ^1H NMR (CD_3OD) δ 8.01 (1H, d), 7.74 (1H, dd), 7.58 (1H, d), 7.45-7.35 (1H, m), 5.25-5.15 (1H, m), 5.05-4.90 (1H, m), 4.60-4.45 (2H, m), 4.30-4.20 (1H, m), 3.55-3.30 (1H, m), 3.20-3.00 (1H, m), 2.75-2.20 (5H, m), 2.14 (3H, s), 2.20-1.60 (4H). Anal. Calcd for
 30 $\text{C}_{23}\text{H}_{27}\text{N}_5\text{O}_8 \cdot 1.5\text{H}_2\text{O}$: C, 52.27; H, 5.72; N, 13.25. Found:

- 576 -

C, 52.31; H, 5.86; N, 12.85. MS (ES^+) 501 (M^+ , 26%), 500 ($\text{M}^+ - 1$, 100), 328 (2), 149 (3), 113 (3).

[3*S*(1*S*,9*S*)] 3-[4-(Hydroxybenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-

5 pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (456), was prepared by a similar method as compound 214e to afford a white solid (0.73g, 72%): mp. >260°C; $[\alpha]_{\text{D}}^{20}$ -66° (c 0.34, MeOH); IR (KBr) 3401, 2946, 1651, 1609, 1584, 1506, 1426, 1277, 1257, 10
1177; ^1H NMR (D_6 -DMSO) δ 10.2 (1H, very bs), 9.17 (1H, bs), 8.65 (1H, s), 8.37 (1H, d, *J* 5.4), 7.81 (2H, d, *J* = 8.2), 6.87 (2H, d, *J* = 8.4), 5.24 (1H, m), 4.92-4.86 (1H, m), 4.41-4.32 (2H, m), 3.68-3.21 (3H, m), 3.12-2.79 (1H, m), 2.50-1.42 (7H, m). MS (ES^+) 459.

15 [3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-9-(indol-2-oylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (475), was prepared by a similar method to that described for compound 214e to afford a
20 white solid (79%): mp. 150°C (softens) 190-210°C; $[\alpha]_{\text{D}}^{23}$ -97.5° (c 0.1, CH_3OH); IR (KBr) 3319, 1658, 1650, 1549, 1421, 1256; ^1H NMR (CD_3OD) δ 7.61 (1H, d, *J* = 8.0), 7.43 (1H, d, *J* = 8.1), 7.21 (2H, m), 7.05 (1H, m), 5.21 (1H, m), 5.07-4.77 (1H, m), 4.54 (2H, m), 4.23 (1H, m),
25 3.46 (1H, m), 3.14 (1H, m), 2.66-1.71 (9H, m). MS (ES^+ , *m/z*), 482 ($\text{M}^+ - 1$, 100%).

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-9-(2-toluoylamino)-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (404), was prepared by

- 577 -

a similar method as compound **214e** to afford a white solid (0.79g, 86%): mp. 156-9°C; $[\alpha]_D^{25}$ -119.7° (c 0.1, CH₃OH); IR (KBr) 3700-2500 (br), 3387, 3309, 2956, 1785, 1659, 1650, 1535, 1422, 1278; ¹H NMR (CD₃OD) δ 7.46-7.15 (4H, m), 5.25-5.15 (1H, m), 5.02-4.90 (1H, m), 4.58-4.45 (2H, m), 4.30-4.20 (1H, m), 3.55-3.30 (1H, m), 3.20-3.05 (1H, m), 2.80-2.20 (4H, m), 2.41 (3H, s), 2.20-1.60 (5H, m). MS (ES⁺) 458 (M⁺, 27%), 457 (M⁺ - 1, 100), 413 (13), 339 (8), 285 (5), 134 (6), 127 (11). Accurate mass calculated for C₂₂H₂₇N₄O₇ (MH⁺): 459.1880. Found 459.1854.

[3S(1S,9S)] 3-{6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-9-[4-(phenylacetamido)benzamido]-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido}-4-oxobutanoic acid (486), was prepared by a similar method as compound **214e** to afford a white solid (325mg, 89%): mp. 165-9°C; $[\alpha]_D^{22}$ -69.1° (c 0.1, CH₃OH); IR (KBr) 3700-2500 (br), 3318, 1658, 1599, 1530, 1505, 1407, 1258; ¹H NMR (CD₃OD) δ 7.85 (2H, d), 7.69 (2H, d), 7.38-7.20 (5H, m), 5.25-5.15 (1H, m), 5.05-4.90 (1H, m), 4.57-4.45 (2H, m), 4.30-4.20 (1H, m), 3.70 (2H, s), 3.55-3.30 (1H, m), 3.20-3.00 (1H, m), 2.75-1.60 (9H, m). Anal. Calcd for C₂₉H₃₁N₅O₈·1.5H₂O: C, 57.61; H, 5.67; N, 11.58. Found: C, 57.81; H, 5.74; N, 11.47. MS (ES⁺) 577 (M⁺, 33%), 576 (M⁺ - 1, 100), 502 (2).

[3S(1S,9S)] 3-{6,10-Dioxo-9-[4-(3-methylbutan-1-oylamino)benzamido]-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido}-4-oxobutanoic acid (487), was prepared by a similar

- 578 -

method as compound **214e** to afford a white foamy solid (335mg, 93%): mp. 176-80°C; $[\alpha]_D^{22}$ -88.0° (c0.1, CH₃OH); IR (KBr) 3700-2500 (br), 3321, 2960, 1781, 1660, 1597, 1529, 1407, 1258, 1187; ¹H NMR (CD₃OD) δ 7.86 (2H, d), 7.69 (2H, d), 5.25-5.15 (1H, m), 5.05-4.90 (1H, m), 4.60-4.45 (2H, m), 4.30-4.20 (1H, m), 3.57-3.30 (1H, m), 3.20-3.00 (1H, m), 2.75-1.60 (12H, m), 1.00 (6H, d). Anal. Calcd for C₂₆H₃₃N₅O₈•H₂O: C, 55.61; H, 6.28; N, 12.45. Found: C, 56.00; H, 6.37; N, 12.15. MS (ES⁺) 543 (M⁺, 31%), 542 (M⁺ - 1, 100), 498 (2), 468 (3).

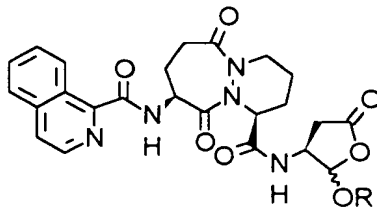
[3S(1S,9S)] 3-[6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-9-(3,4,5-trimethoxybenzoylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (417), was prepared by a similar method to that described for compound **214e** to afford a white solid (0.63g, 92%): mp. 145-155°C (approx., not sharp); $[\alpha]_D^{27}$ -114.6° (c 0.11, CH₃OH); IR (KBr) 3327, 1658, 1586, 1548, 1501, 1416, 1341, 1238, 1126; ¹H NMR (CD₃OD) δ 7.22 (2H, s), 5.21 (1H, m), 5.00 (1H, m), 4.56, 4.49 (2H, 2m), 4.25 (1H, m), 3.88 (6H, s), 3.80 (3H, s), 3.55-3.43 (1H, m), 3.12 (1H, m), 2.71-1.70 (9H, m). Anal. Calcd for C₂₄H₃₀N₄O₁₀•2H₂O: C, 50.52; H, 6.01; N, 9.82. Found: C, 50.49; H, 6.05; N, 9.68. MS (ES⁺, m/z) 533 (M⁺ - 1, 100%).

[3S(1S,9S)] 3-[6,10-Dioxo-9-(naphth-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (408), was prepared by a similar method to that described for compound **214e** to afford a

- 579 -

white solid (73%): mp. 157-165°C (not sharp); $[\alpha]_D^{27}$ - 140.5° (c 0.1, CH₃OH); IR (KBr) 3325, 1658, 1531, 1420, 1278, 1257; ¹H NMR (CD₃OD) δ 8.33-8.28 (1H, m), 8.01-7.78 (2H, m), 7.71 (1H, d, J = 6.0), 7.59-7.52 (3H, m), 5.27 (1H, m), 5.12-5.03 (1H, m), 4.55 (2H, m), 4.25 (1H, m), 3.64-3.43 (1H, m), 3.24-3.12 (1H, m), 2.80-1.67 (9H, m). Anal. Calcd for C₂₅H₂₆N₄O₇•2H₂O: C, 56.60; H, 5.70; N, 10.56. Found: C, 56.70; H, 5.80; N, 10.33. MS (ES⁺, m/z), 493 (M⁺ - 1, 100%).

10 [3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-4-(hydroxy-3,5-dimethylbenzoyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (214w), was prepared by a similar method as compound 214e to afford 210mg (62%) of a
 15 white solid: mp. >260°C; $[\alpha]_D^{20}$ -93° (c 0.20, MeOH); IR (KBr) 3401, 2948, 1651, 1604, 1559, 1486, 1421, 1325, 1276, 1210; ¹H NMR (D₆-DMSO) δ 9.39 (1H, bs), 8.29 (1H, d, J = 5.9), 7.55 (2H, s), 6.64 (1H, d, J = 6.1), 5.79 (1H, s), 5.25-5.21 (1H, m), 1.90-1.82 (1H, m), 4.41-
 20 3.69 (2H, m), 3.47-3.20 (3H, m), 2.97-2.91 (1H, m), 2.23 (6H, s), 2.25-1.60 (7H, m).



550q R= Et

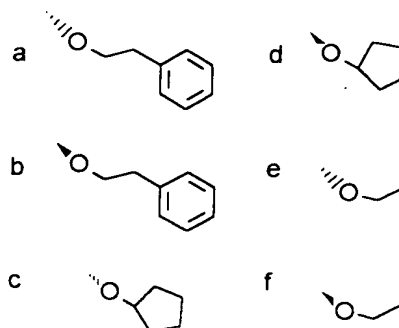
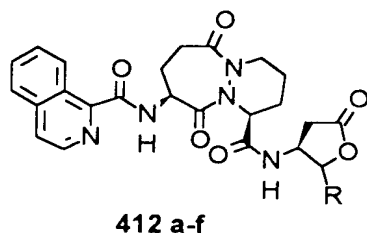
213y R= Bn

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Ethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-

- 580 -

octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550q), was synthesized via methods used to prepare 213e to afford 550q.

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzylloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213y), was synthesized via methods used to prepare 213e to afford 213y.



[1*S*,9*S*(2*S*,3*S*)] N-(2-Phenethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (412a) was synthesized via methods used to prepare 550q using 513a-1 to afford 412a.

[1*S*,9*S*(2*R*,3*S*)] N-(2-Phenethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (412b) was synthesized via

- 581 -

methods used to prepare 550q using 513a-2 to afford 412b.

[1*S*, 9*S*(2*S*, 3*S*)] N-(2-Cyclopentoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-
5 1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (412c)
was synthesized via methods used to prepare 550q using 513b-1 to afford 412c.

[1*S*, 9*S*(2*R*, 3*S*)] N-(2-Cyclopentoxy-5-oxotetrahydrofuran-
10 3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-
1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (412d)
was synthesized via methods used to prepare 550q using 513b-2 to afford 412d: ¹H NMR (CDCl₃) δ 9.5 (1H, d),
15 8.9 (1H, d), 8.5 (1H, d), 7.9-7.8 (2H, m), 7.8-7.65 (2H, m), 6.55 (1H, d), 5.55 (1H, d), 5.25-5.1 (2H, m),
4.75-4.65 (1H, m), 4.65-4.6 (1H, m), 4.4-4.3 (1H, m), 3.25-3.15 (1H, m), 3.15-3.05 (1H, m), 2.95-2.8 (2H, m),
2.55-2.4 (2H, m), 2.15-1.5 (14H, m).

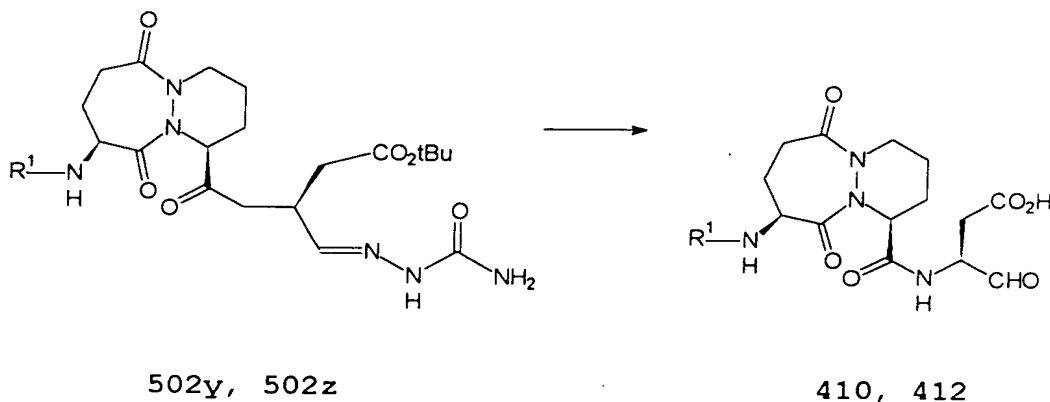
20 [1*S*, 9*S*(2*S*, 3*S*)] N-(2-Ethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2] diazepine-1-carboxamide, (412e) was synthesized via methods used to prepare 550q using 513f-1 to afford 412e.

25 [1*S*, 9*S*(2*R*, 3*S*)] N-(2-Ethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2] diazepine-1-

- 582 -

carboxamide, (412f) was synthesized via methods used to prepare 550q using 513f-2 to afford 412f.

Compounds 410 and 412 were prepared via methods used to prepare 605 from 604.



compound	R ¹
502y, 410	
502z, 412	

10 [3S(1S,9S)] 3-[(6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-9-(thiophene-3-yl-carbonylamino)-1-carboxamido]-4-oxobutanoic acid (410),
 was purified by flash chromatography (5-25% methanol in dichloromethane) to give 296mg (94%) of a colourless
 solid: mp. 90-200°C; IR (KBr) 3338, 3096, 2950, 1787,
 15 1726, 1657, 1546, 1420, 1279, 1258, 1125, 1092, 984,

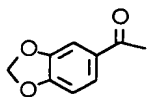

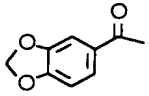
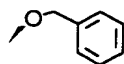
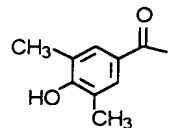
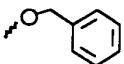
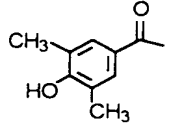
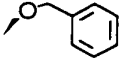
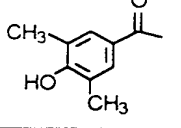
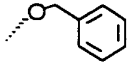
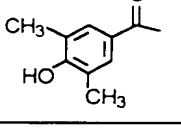
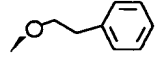
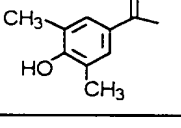
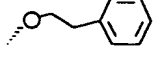
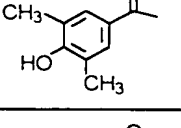
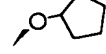
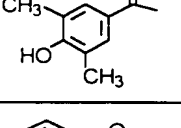
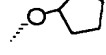
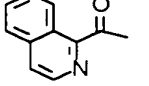
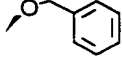
- 583 -

933; ^1H NMR (CD_3OD) δ 8.41 (1H, d), 8.13 (1H, d), 7.54-7.41 (3H, m), 7.20 (1H, d), 5.19-5.11 (1H, m), 4.54-4.30 (1H, m), 3.27 (1H, m), 3.18-3.03 (1H, m), 2.81-2.64 (2H, m), 2.56-1.59 (7H, m). Anal. Calcd for $\text{C}_{19}\text{H}_{22}\text{N}_4\text{O}_7\text{S} \cdot 2.5\text{H}_2\text{O}$: C, 46.05; H, 5.49; N, 11.31. Found: C, 46.36; H, 5.25; N, 11.10. MS (ES^+) 449 ($\text{M} - 1$, 80%), 113 (100). Accurate mass calculated for $\text{C}_{19}\text{H}_{23}\text{N}_4\text{O}_7\text{S}$ (MH^+): 451.1287. Found: 451.1295.

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (412) was prepared by a similar method to that described for compound 605 to afford a white glassy solid (69%): mp. 138-141°C; $[\alpha]_{\text{D}}^{23}$ -105.5° (c 0.5, CH_2Cl_2); IR (KBr) 3375, 1787, 1659, 1515, 1421, 1278, 1256; ^1H NMR (CDCl_3) δ 9.32 (1H, m), 8.79 (1H, m), 8.47 (1H, m), 7.86-7.64 (4H, m), 5.31, 5.18, 4.59, 4.37 (4 or 5H, m), 3.55-2.76, 2.49-2.39, 2.05, 1.65 (11H, 4m). Anal. Calcd for $\text{C}_{24}\text{H}_{25}\text{N}_5\text{O}_7 \cdot 1.5\text{H}_2\text{O}$: C, 55.17; H, 5.40; N, 13.40. Found: C, 54.87; H, 5.22; N, 13.15. MS (ES^+ , m/z) 494 ($\text{M}^+ - 1$, 100%).

[3*S*(1*S*,9*S*)] *t*-Butyl 3-[6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-9-(thiophene-3-yl)-6H-pyridazino[1,2-*a*][1,2]diazepine-carbonylamino)-1-carboxamido]-4-oxobutanoate semicarbazone (502y), was synthesized via methods used to prepare 604 from 603 to afford a pale cream powder: mp. 120-180°C; $[\alpha]_{\text{D}}^{23}$ -109° (c 0.18, CH_2Cl_2); IR (KBr) 3478, 3327, 1670, 1582, 1543, 1421, 1279, 1257, 1155; ^1H NMR (CDCl_3 , CD_3OD) δ 8.04 (1H, m), 7.49 (1H, m), 7.38 (1H, m), 7.17 (1H, m),

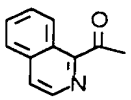
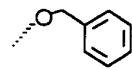
- 585 -

compound	R ⁴	R ¹
415b		
415c		
214w-1		
214w-2		
214w-3		
214w-4		
214w-5		
214w-6		
214w-7		
412g		

5

10

- 586 -

compound	R ⁴	R ¹
412h		

5 [1*S*,9*S*(2*S*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (415a) was synthesized via methods used to prepare 550q to afford 415a.

10 [1*S*,9*S*(2*RS*,3*S*)] N-(2-Ethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(methylenedioxy benzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (415b) was synthesized via methods used to prepare 550q to afford 415b.

15 [1*S*,9*S*(2*R*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(methylenedioxy benzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (415c) was synthesized via methods used to prepare 550q to afford 415c.

20 [1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (214w-1) was synthesized via methods used to prepare 550q to afford 214w-1.

[1*S*,9*S*(2*R*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-

- 587 -

1,2,3,4,7,8,9,10-octahydro-6-H-
pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (214w-2)
was synthesized via methods used to prepare 550q to
afford 214w-2.

5 [1*S*,9*S*(2*S*,3*S*)] N-(2-Benzylloxy-5-oxotetrahydrofuran-3-
yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-
1,2,3,4,7,8,9,10-octahydro-6-H-
pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (214w-3)
was synthesized via methods used to prepare 550q to
10 afford 214w-3.

[1*S*,9*S*(2*R*,3*S*)] N-(2-Phenethoxy-5-oxotetrahydrofuran-3-
yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-
1,2,3,4,7,8,9,10-octahydro-6-H-
pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (214w-4)
15 was synthesized via methods used to prepare 550q to
afford 214w-4.

[1*S*,9*S*(2*S*,3*S*)] N-(2-Phenethoxy-5-oxotetrahydrofuran-3-
yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-
1,2,3,4,7,8,9,10-octahydro-6-H-
20 pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (214w-5)
was synthesized via methods used to prepare 550q to
afford 214w-5.

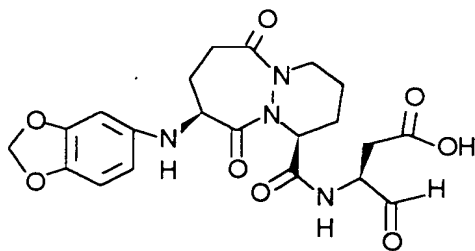
[1*S*,9*S*(2*R*,3*S*)] N-(2-Cyclopentoxo-5-oxotetrahydrofuran-
3-yl)-6,10-dioxo-9-(3,5-dimethyl-4-
25 hydroxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-
pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (214w-6)
was synthesized via methods used to prepare 550q to
afford 214w-6.

- 588 -

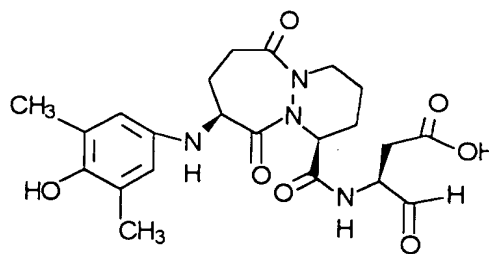
[1*S*,9*S*(2*S*,3*S*)] N-(2-Cyclopentoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide, (214w-7) was synthesized via methods used to prepare 550q to afford 214w-7.

[1*S*,9*S*(2*R*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide, (412g) was synthesized via methods used to prepare 550q to afford 412g.

[1*S*,9*S*(2*S*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide, (412h) was synthesized via methods used to prepare 550q to afford 412h.



415

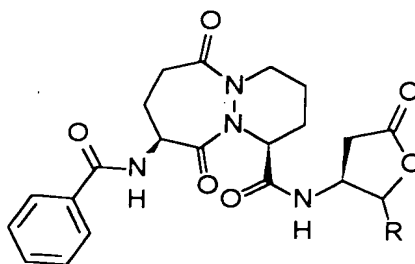


214w

[3*S*(1*S*,9*S*)] 3-(9-(4,5-Methylenedioxybenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (415), was synthesized by the method used to prepare 2002 from 2001 to afford 415.

- 589 -

[3*S*(1*S*,9*S*)]3-(9-(3,5-Dichloro-4-hydroxybenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (214*w*), was synthesized by the method used to prepare 2002 from 2001 to afford 214*w*.

2100*k-o*

compound	R
2100 <i>k</i>	
2100 <i>l</i>	
2100 <i>m</i>	
2100 <i>n</i>	
2100 <i>o</i>	

- 590 -

[1*S*,9*S*(2*RS*,3*S*)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-*N*-(2-phenethyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide (2100k),

5 was prepared by a similar method as compound 213e to afford a mixture of diastereoisomers (75/25) as a white solid (258mg, 83%): mp. 101°C; $[\alpha]_D^{25}$ -96° (c 0.2, CH₂Cl₂); IR (KBr) 3328, 2935, 2978, 1732, 1669, 1603, 1483, 1450, 1414, 1237, 1155, 1082, 989, 755; ¹H NMR
 10 (CDCl₃) δ 7.84-7.80 (2H, m), 7.54-7.17 (8H, m), 7.06-6.99 (1H, m), 6.25 (1H, d, *J* = 7.9H), 5.41 (0.75H, d, *J* = 5.4H), 5.31 (0.25H, bs), 5.23-5.09 (1H, m), 4.93-4.87 (1H, m), 4.68-4.51 (2H, m), 4.40-4.33 (0.25H, m), 4.24-4.14 (0.75H, m), 3.95-3.70 (1H, m), 3.30-3.13 (1H, m),
 15 3.14-2.78 (5H, m), 2.47-2.21 (2H, m), 2.05-1.50 (5H, m). Anal. Calcd for C₂₉H₃₂N₄O₇•0.5H₂O: C, 62.47; H, 5.97; N, 10.05. Found: C, 62.17; H, 5.83; N, 9.97. MS (ES⁺) 549.

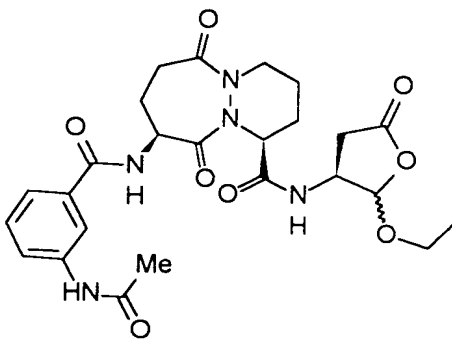
[1*S*,9*S*(2*RS*,3*S*)] 9-Benzamido-*N*-(2-cyclopentyloxy-5-oxo-tetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide (2100l), was prepared by a similar method
 20 as 213e, (74%) as a colourless solid: mp. 172-80°C; $[\alpha]_D^{23}$ -91.5° (c 0.1, CH₂Cl₂); IR (KBr) 3290, 1792, 1677, 1657, 1642, 1544, 1425, 1280, 1259, 1124, 977; ¹H
 25 NMR (CDCl₃) δ 7.80 (2H, m), 7.46 (3.5H, m), 7.00 (1H, d, *J* = 6.7), 6.48 (0.5H, d, *J* = 7.9), 5.55 (0.5H, d, *J* = 5.3), 5.19 (2H, s + m), 4.93 (0.5H, m), 4.62 (1.5H, m), 4.34 (1H, m), 4.18 (0.5H, m), 3.28-2.70 (4H, m), 2.49-
 30 2.29 (2H, m), 2.05-1.48 (15H, m).

- 591 -

- [1*S*,9*S*(2*R*,3*S*)] 9-Benzamido-6,10-dioxo-N-[2-(2-indanyloxy)-5-oxo-tetrahydrofuran-3-yl]-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100m),
 5 was prepared by a similar method as 213e, (76%) as a colourless solid: mp. ~140°C, remelts 187-9°C; $[\alpha]_D^{23}$ -96.9° (c 0.11, CH₂Cl₂); IR (KBr) 3507, 3308, 3251, 1772, 1660, 1641, 1566, 1545, 1457, 1424, 1346, 1326, 1302, 1275, 1258, 1136, 1085, 1018, 981; ¹H NMR (CDCl₃)
 10 δ 7.78 (2H, m), 7.53 (3H, m), 7.19 (4H, m), 6.91 (1H, d, J = 7.4), 6.27 (1H, d, J = 7.6), 5.66 (1H, d, J = 5.3), 5.10 (1H, m), 4.96 (1H, m), 4.75 (2H, m), 4.52 (1H, m), 3.08 (3H, m), 3.03-2.71 (5H, m), 2.48-2.31 (2H, m), 1.90-1.40 (4H, m), 1.22 (1H, m).
- 15 [1*S*,9*S*(2*S*,3*S*)] 9-Benzoylamino-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100n), was prepared by a similar method to that described for compound 213e to afford a white
 20 glassy solid (76%): mp. 112-5°C; $[\alpha]_D^{23}$ -62.0° (c 0.1, CH₂Cl₂); IR (KBr) 3305, 1789, 1677, 1665, 1535, 1422, 1279, 1256, 1119, 942, 700; ¹H NMR (CDCl₃) δ 7.84 (2H, m), 7.58-7.27 (9H, m), 6.99 (1H, d, J = 7.8), 5.23 (1H, s), 5.23-5.11 (1H, m), 4.89 (1H, m), 4.76 (1H, d, J =
 25 11.3), 4.55 (1H, d, J = 11.4), 4.58-4.43 (2H, m), 3.30-2.96, 2.81-2.69, 2.46-2.37, 2.16-1.66 (10H, 4m), 2.27 (1H, d, J = 17.8). Anal. Calcd for C₂₈H₃₀N₄O₇•0.5H₂O: C, 61.87; H, 5.75; N, 10.32. Found: C, 61.88; H, 5.70; N, 10.33. MS (ES⁺, m/z) 535 (M⁺ + 1, 100%).

- 592 -

[1*S*,9*S*(2*R*,3*S*)] 9-Benzoylamino-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100o), (containing about 7% of (2*S*)), was prepared by a similar method to that described for compound 213e to afford a white glassy solid (81%): mp. 115-7°C; $[\alpha]_D^{23}$ -121.8° (c 0.11, CH₂Cl₂); IR (KBr) 3326, 1792, 1659, 1535, 1421, 1278, 1257, 1124, 978; ¹H NMR (CDCl₃) δ 7.82 (2H, m), 7.58-7.24 (8H, m), 6.90 (1H, d, J = 7.3), 6.49 (1H, d, J = 7.7), 5.57 (1H, d, J = 5.5), 5.11 (2H, m), 4.91 (1H, d, J = 11.4), 4.57 (1H, d, J = 11.1), 4.81-4.68 (1H, m), 4.65-4.54 (1H, m), 3.18-2.71 2.52-2.30, 2.05-1.62 (11H, 3m). Anal. Calcd for C₂₈H₃₀N₄O₇•0.5H₂O: C, 61.87; H, 5.75; N, 10.32. Found: C, 61.70; H, 5.71; N, 10.15. MS (ES⁺, m/z) 535 (M⁺ + 1, 94.3%), 557 (100%).



550n

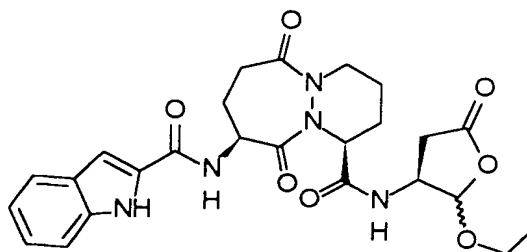
[1*S*,9*S*(2*RS*,3*S*)] 9-(3-Acetamido)benzoylamino-6,10-dioxo-N-(2-ethoxy-5-oxo-tetrahydrofuran-3-yl)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550n), was prepared by a similar method as compound 213e to

- 593 -

afford a mixture of diastereoisomers (65/35) as a tan powder (390mg, 28%): mp. 139-145°C; $[\alpha]_D^{23}$ -104° (c 0.2, MeOH); IR (KBr) 3318, 2405, 2369, 1792, 1660, 1591, 1549, 1484, 1422, 1257, 1117; ^1H NMR (D_6 -DMSO) δ

5 10.1 (1H, s), 8.80 (0.65H, d, J = 6.6), 8.58 (0.35H, d, J = 6.6), 8.59 (1H, d, J = 7.0), 8.06 (1H, bs), 7.83-7.79 (1H, m), 7.61-7.57 (1H, m), 7.47-7.39 (1H, m), 5.61 (0.35H, d, J = 5.0), 5.37 (0.65H, bs), 5.17-5.14 (0.35H, m), 5.08-5.06 (0.65H, m), 4.92-4.86 (1H, m),

10 4.67-4.61 (0.35H, m), 4.47-4.41 (0.65H, m), 4.28-4.11 (1H, 2m), 3.80-3.59 (2H, m), 3.23-2.75 (3H, m), 2.61-1.48 (7H, m), 2.10 (3H, s), 1.25 and 1.17 (3H, 2t, J = 5.8). MS (ES^+) 528.



550o

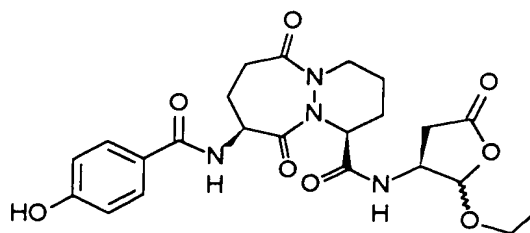
15 **[1S,9S(2RS,3S)] 6,10-Dioxo-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-9-(2-indoloylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550o),**

was synthesized by a similar method as compound 213e to

20 afford a colourless solid (1.071g, 80%): mp. 155-70°C; $[\alpha]_D^{22}$ -75.8° (c 0.26, CH_2Cl_2); IR (KBr) 3314, 2941, 1791, 1658, 1545, 1420, 1341, 1312, 1252, 1181, 1118, 939, 749; ^1H NMR (CDCl_3) δ 9.45 (0.5H, s), 9.34 (0.5H, s), 7.68-7.62 (1H, m), 7.49-7.39 (2H, m), 7.33-7.26

- 594 -

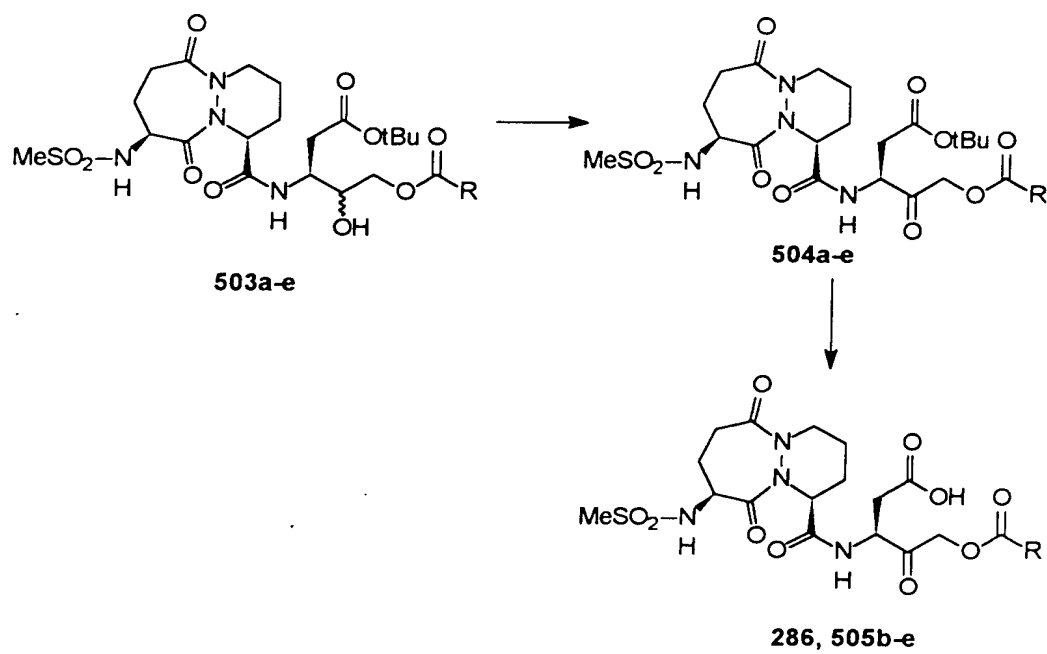
(1H, m), 7.18-7.03 (3H, m), 5.49 (0.5H, d), 5.30 (0.5H, s), 5.26-5.13 (1H, m), 4.90-4.83 (0.5H, m), 4.76-4.49 (1H, m), 4.42-4.35 (0.5H, m), 3.97-3.74 (1H, m), 3.72-3.53 (1H, m), 3.35-2.64 (4H, m), 2.50-2.37 (1H, m), 2.20-1.82 (5H, m), 1.69-1.50 (2H, m), 1.30-1.19 (3H, m).

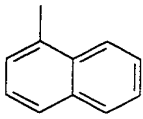
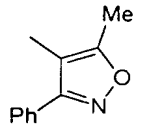
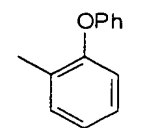
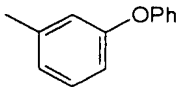


550p

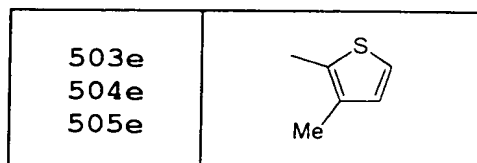
[1*S*,9*S*(2*RS*,3*S*)] 6,10-Dioxo-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-9-(4-hydroxybenzoyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550p), was prepared by a similar method as compound 213e to afford a mixture of diastereoisomers as a white foam (820mg, 47%): $[\alpha]_D^{24}$ -75° (c 0.16, CH₂Cl₂); IR (KBr) 3401, 2937, 1791, 1657, 1609, 1539, 1505, 1423, 1277, 1177, 1118; ¹H NMR (CDCl₃) δ 8.07-8.05 (1H, m), 7.67 (2H, d, J = 7.9), 7.38-7.29 (2H, m), 6.80 (2H, d, J = 8.5), 5.49 (0.5H, d, J = 4.6), 5.23 (0.5H, bs), 5.24-5.20 (1H, m), 5.12-5.08 (1H, m), 4.68-4.29 (2H, m), 3.92-3.45 (3H, m), 3.32-2.30 (2H, m), 2.80-1.56 (11H, m), 1.21 (3H, t, J = 7.0H).

- 595 -



compound	R
503a 504a 286	
503b 504b 505b	
503c 504c 505c	
503d 504d 505d	

- 596 -



[3*S*,4*R*(1*S*,9*S*)] t-Butyl 3-(6,10-dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-4-hydroxy-5-(1-naphthoyloxy)pentanoate (503a), was prepared from **212b** and (3*S*,4*R*) t-butyl (N-allyloxycarbonyl)-3-amino-4-hydroxy-5-(1-naphthoyloxy)pentanoate by the method described for (**213e**) to afford 533mg (81%) of an off-white foam: $[\alpha]_D^{22} -81.4^\circ$ (c 0.5, CH₂Cl₂); IR(KBr) 3342, 2976, 1719, 1664, 1328, 1278, 1246, 1153, 1137. ¹H NMR (CDCl₃) δ 8.86 (1*H*, d, *J* = 8.4), 8.21 (1*H*, dd, *J* = 1.3, 7.3), 8.03 (1*H*, d, *J* = 8.1), 7.88 (1*H*, d, *J* = 8.6), 7.66-7.45 (3*H*, m), 7.23 (1*H*, d, *J* = 8.6), 5.96 (1*H*, d, *J* = 9.2), 5.30 (1*H*, m), 4.59-4.33 (5*H*, m), 4.24 (1*H*, m), 3.96 (1*H*, brd), 3.29 (1*H*, m), 2.95 (1*H*, m), 2.93 (3*H*, s), 2.69-2.50 (3*H*, m), 2.36 (1*H*, m), 1.96 (4*H*, m), 1.62 (1*H*, m), 1.41 (9*H*, s). Anal. Calcd for C₃₁H₄₀N₄O₁₀S•0.25H₂O : C, 55.97; H, 6.14; N, 8.42. Found: C, 55.90; H, 6.11; N, 8.23. M.S. (ES⁺) 683 (M+Na, 100%), 661 (M+1,39), 605 (78).

[3*S*(1*S*,9*S*)] t-Butyl 3-(6,10-dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-5-(1-naphthoyloxy)-4-oxopentanoate (504a), was synthesized from **503a** via method used to prepare **216e** from **215e** to afford 446mg (91%) of a colourless foam: $[\alpha]_D^{21} -111.6^\circ$

- 597 -

(c 0.5, CH₂Cl₂); IR (KBr) 3319, 2978, 2936, 1723, 1670, 1413, 1370, 1329, 1278, 1246, 1153. ¹H NMR (CDCl₃) δ 8.87 (1H, d, J = 8.9), 8.29 (1H, d, J = 7.2), 8.06 (1H, d, J = 8.3), 7.90 (1H, d, J = 8.2), 7.66-7.48 (3H, m), 7.37 (1H, d, J = 8.1), 5.61 (1H, d, J = 9.0), 5.31 (1H, m), 5.22 (1H, AB, J = 16.9), 5.09 (1H, AB, J = 16.92), 4.99 (1H, m), 4.65-4.43 (2H, m), 3.28 (1H, m), 2.96 (3H, s), 2.86 (2H, m), 2.59 (1H, m) 2.38 (1H, dd, J = 6.8, 13.2), 2.21-1.70 (6H, m), 1.45 (9H, s). Anal.

10 Calcd for C₃₁H₃₈N₄O₁₀S•0.25H₂O. C, 56.14; H, 5.85; N, 8.45. Found: C, 56.11; H, 5.83; N, 8.29. M.S. (ES⁺) 657 (M-1, 100%).

[3*S*(1*S*,9*S*)] 3-(6,10-Dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-5-(1-naphthoyloxy)-4-oxopentanoic acid (286), was prepared from 504a by the method described for 217 to afford 356mg (93%) of a white powder: mp 120-123°C; [α]_D²³ -121° (c 0.194, CH₂Cl₂); IR (KBr) 3314, 2937, 1722, 1663, 1412, 1328, 1278, 1245, 1195, 1132. ¹H NMR (d6-DMSO) δ 12.63 (1H, brs), 8.94 (1H, d, J = 7.4), 8.78 (1H, d, J = 8.6), 8.26 (2H, m), 8.11 (1H, d, J = 8.0), 7.77-7.62 (4H, m), 5.28 (2H, s), 5.21 (1H, m), 4.82 (1H, m), 4.44-4.29 (2H, m), 3.31 (1H, m), 2.98 (3H, s), 2.98-2.86 (2H, m), 2.72 (1H, dd, J = 7.3, 16.9), 2.40 (1H, m), 2.24-1.84 (4H, m), 1.69 (2H, m). Anal. Calcd for C₂₇H₃₀N₄O₁₀S•H₂O : C, 52.25; H, 5.20; N, 9.03. Found: C, 52.11; H, 4.97; N, 8.89. M.S. (ES⁺) 601 (M-1, 100%).

30 [3*S*,4*RS*(1*S*,9*S*)] t-Butyl 3-[6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-9-

- 598 -

(methanesulphonylamino)-1-carboxamido]-4-hydroxy-5-(5-methyl-3-phenylisoxazoyloxy)pentanoate (503b), was synthesized by a similar method as compound 213e, to afford an off-white powder (671mg, 88%): mp. 90-120°C; IR (KBr) 3345, 2977, 1727, 1664, 1532, 1450, 1423, 1369, 1323, 1310, 1276, 1257, 1154, 1101, 990, 766; ¹H NMR (CDCl₃) δ 7.61-7.55 (2H, m), 7.51-7.42 (3H, m), 6.86 (1H, d), 5.69 (1H, d), 5.21 (1H, m), 4.64-4.38 (2H, m), 4.15-4.05 (3H, m), 3.84 (1H, s), 3.31-3.14 (2H, m), 2.97-2.87 (1H, m), 2.94 (3H, s), 2.76 (3H, s), 2.64-2.48 (3H, m), 2.39-2.29 (1H, m), 2.04-1.61 (5H, m). Anal. Calcd for C₃₁H₄₁N₅O₁₁S·H₂O: C, 52.46; H, 6.11; N, 9.87; S, 4.52. Found: C, 52.34; H, 5.92; N, 9.56; S, 4.44. MS (ES⁺) 714 (47%), 692 (M⁺ + 1, 84), 636 (100).

15 [3S(1S,9S)] t-Butyl 3-[6,10-dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-5-(5-methyl-3-phenylisoxazoyloxy)-4-oxopentanoate (504b), was synthesized by a similar method as compound 216b to afford a colourless powder (601mg, 93%): mp. 75-115°C; [α]_D²³ -104° (c 0.26, CH₂Cl₂); IR (KBr) 3324, 2977, 2935, 1730, 1670, 1525, 1452, 1422, 1369, 1317, 1276, 1256, 1222, 1155, 1107, 990, 766; ¹H NMR (CDCl₃) δ 7.68-7.61 (2H, m), 7.47-7.38 (3H, m), 7.32-7.24 (1H, m), 5.56 (1H, d), 5.36-5.24 (1H, m), 5.04 (1H, d), 4.88 (1H, d), 4.86-4.77 (1H, m), 4.64-4.39 (2H, m), 3.32-3.17 (1H, m), 2.97-2.85 (1H, m), 2.93 (3H, s), 2.76 (3H, s), 2.80-2.71 (1H, m), 2.65-2.49 (1H, m), 2.41-2.30 (1H, m), 2.12-1.61 (6H, m), 1.42 (9H, s). Anal. Calcd for C₃₁H₃₉N₅O₁₁S·H₂O: C, 52.61; H, 5.84; N, 9.90; S, 4.53. Found: C, 52.94; H, 5.69; N, 9.72; S, 4.51.

- 599 -

MS (ES^+) 712 (31%), 707 (100), 690 ($\text{M}^+ + 1$, 41), 634 (55).

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido]-5-(5-methyl-3-phenylisoxazoyloxy)-4-oxopentanoic acid (505b), was synthesized by a similar method as compound 217 to afford a colourless powder (499mg, 96%): mp. 95-145°C; $[\alpha]_{\text{D}}^{22}$ -137° (c 0.12, MeOH); IR (KBr) 3323, 2936, 1732, 1665, 1529, 1452, 1421, 1312, 1275, 1256, 1221, 1183, 1153, 1135, 1101, 990; ^1H NMR (CD_3OD) δ 7.67-7.56 (2H, m), 7.49-7.38 (4H, m), 5.23-5.12 (1H, m), 5.02 (1H, d), 4.79-4.73 (1H, m), 4.52-4.34 (3H, m), 3.48-3.25 (2H, m), 3.03-2.85 (2H, m), 2.94 (3H, s), 2.74 (3H, s), 2.79-2.66 (1H, m), 2.52-2.38 (1H, m), 2.29-2.14 (1H, m), 2.04-1.70 (4H, m). Anal. Calcd for $\text{C}_{27}\text{H}_{31}\text{N}_5\text{O}_{11}\text{S}\cdot\text{H}_2\text{O}$: C, 49.77; H, 5.18; N, 10.75; S, 4.92. Found: C, 49.83; H, 5.01; N, 10.27; S, 4.84. MS (ES^+) 746 (42%), 632 ($\text{M} - 1$, 100), 386 (60). Accurate mass calculated for $\text{C}_{27}\text{H}_{32}\text{N}_5\text{O}_{11}\text{S}$ (MH^+): 634.1819. Found: 634.1807.

[3*S*,4*RS*(1*S*,9*S*)] *t*-Butyl 3-[6,10-dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido]-4-hydroxy-5-(2-phenoxybenzoyloxy)pentanoate (503c), was synthesized by a similar method as compound 213e to afford a colourless solid (446mg, 84%): IR (KBr) 3345, 2976, 2935, 1727, 1664, 1603, 1535, 1483, 1451, 1416, 1395, 1369, 1328, 1297, 1277, 1237, 1155, 1135, 1076, 990, 755; ^1H NMR (CDCl_3) δ 7.98-7.89 (1H, m), 7.55-7.45

- 600 -

(1H, m), 7.39-7.18 (3H, m), 7.14-7.07 (1H, m), 7.00-6.90 (3H, m), 6.75 (1H, d), 5.57-5.50 (1H, m), 5.21-5.09 (1H, m), 4.64-4.42 (2H, m), 4.36-4.12 (3H, m), 3.95-3.87 (1H, m), 3.39-3.18 (1H, m), 3.00-2.82 (1H, m), 2.95 (3H, s), 2.69-2.48 (3H, m), 2.42-2.28 (1H, m), 2.07-1.62 (6H, m), 1.42 (9H, s). Anal. Calcd for $C_{33}H_{42}N_4O_{11}S \cdot H_2O$: C, 54.99; H, 6.15; N, 7.77; S, 4.45. Found: C, 54.95; H, 5.95; N, 7.34; S, 4.20. MS (ES^+) 725 (26%), 720 (47), 703 ($M^+ + 1$, 34), 433 (100), 403 (89).

[3*S*(1*S*,9*S*)] *t*-Butyl 3-[6,10-dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido]-4-oxo-5-(2-phenoxybenzoyloxy) pentanoate (504c), was synthesized by a similar method as compound 216e to afford a colourless powder: mp. 85-100°C; $[\alpha]_D^{22}$ -91.3° (c 0.52, CH_2Cl_2); IR (KBr) 3328, 2978, 2935, 1732, 1669, 1603, 1524, 1483, 1450, 1396, 1369, 1296, 1276, 1237, 1155, 1132, 1082, 989, 755; 1H NMR ($CDCl_3$) δ 8.03-7.98 (1H, m), 7.52-7.44 (1H, m), 7.37-7.07 (5H, m), 7.01-6.92 (3H, m), 5.52 (1H, d), 5.28-5.20 (1H, m), 5.06-4.84 (3H, m), 4.64-4.39 (2H, m), 3.32-3.14 (1H, m), 2.99-2.88 (1H, m), 2.94 (3H, s), 2.65-2.45 (2H, m), 2.39-2.29 (1H, m), 2.12-1.58 (6H, m), 1.40 (9H, s). Anal. Calcd for $C_{33}H_{40}N_4O_{11}S$: C, 56.56; H, 5.75; N, 8.00; S, 4.58. Found: C, 56.37; H, 5.84; N, 7.69; S, 4.37. MS (ES^+) 723 (30%), 718 (100), 701 ($M^+ + 1$, 23), 645 (59).

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido]-4-oxo-5-

- 601 -

(2-phenoxybenzoyloxy)pentanoic acid (505c), was synthesized by a similar method as compound 217 to afford a colourless foam (252mg, 72%): mp. 90-125°C; $[\alpha]_D^{23}$ -133° (c 0.11, MeOH); IR (KBr) 3314, 2938, 1792, 1734, 1663, 1604, 1535, 1483, 1448, 1415, 1250, 1132, 756; ^1H NMR (D_6 -DMSO) δ 8.81-8.76 (1H, m), 7.92 (1H, d), 7.68-7.54 (2H, m), 7.41-7.25 (3H, m), 7.16-6.91 (4H, m), 5.13-4.98 (2H, m), 4.72-4.63 (1H, m), 4.37-4.21 (2H, m), 2.92 (3H, s), 2.90-2.60 (3H, m), 2.35-2.26 (1H, m), 2.17-2.05 (2H, m), 1.99-1.80 (2H, m), 1.61-1.50 (1H, m). Anal. Calcd for $\text{C}_{29}\text{H}_{32}\text{N}_4\text{O}_{11}\text{S} \cdot 0.5\text{H}_2\text{O}$: C, 53.29; H, 5.09; N, 8.57; S, 4.90. Found: C, 53.57; H, 5.18; N, 8.32; S, 4.75. MS (ES^+) 643 ($M - 1$, 100%).

15 [3*S*,4*RS*(1*S*,9*S*)] *t*-Butyl 3-[6,10-dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido]-4-hydroxy-5-(3-phenoxybenzoyloxy) pentanoate (503d), was synthesized by a similar method as compound 213e to afford a colourless solid (563mg, 90%): IR (KBr) 3349, 2978, 2935, 1724, 1664, 1583, 1536, 1489, 1443, 1370, 1327, 1271, 1226, 1189, 1155, 1073, 990, 755; ^1H NMR (CDCl_3) δ 7.77 (1H, d), 7.67 (1H, m), 7.45-7.10 (6H, m), 7.00 (2H, d), 5.93-5.80 (1H, m), 5.36-5.30 (1H, m), 4.63-4.24 (5H, m), 4.15-4.09 (1H, m), 3.37-3.22 (1H, m), 2.98-2.74 (1H, m), 2.94 (3H, s), 2.70-2.47 (3H, m), 2.40-2.30 (1H, m), 2.15-1.60 (5H, m), 1.42 (9H, s). Anal. Calcd for $\text{C}_{33}\text{H}_{42}\text{N}_4\text{O}_{11}\text{S} \cdot \text{H}_2\text{O}$: C, 54.99; H, 6.15; N, 7.77; S, 4.45. Found: C, 54.60; H, 5.88; N, 7.49; S, 4.50. MS (ES^+) 725 (19%), 720 (91), 703 ($M^+ + 1$, 74), 647 (76), 629 (100), 433 (78).

- 602 -

[3S(1S,9S)] t-Butyl 3-[6,10-dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(3-phenoxybenzoyloxy) pentanoate (504d), was

5 synthesized by a similar method as compound 216e to afford a colourless powder (466mg, 85%): mp. 75-100°C; $[\alpha]_D^{22}$ -99.3° (c 0.60, CH₂Cl₂); IR (KBr) 3335, 2978, 2937, 1728, 1669, 1584, 1525, 1487, 1444, 1416, 1369, 1328, 1272, 1227, 1188, 1155, 989, 754; ¹H NMR (CDCl₃) δ
 10 7.82-7.77 (1H, m), 7.66-7.65 (1H, m), 7.46-7.32 (4H, m), 7.26-7.10 (2H, m), 7.04-6.98 (2H, m), 5.68 (1H, d), 5.37-5.31 (1H, m), 5.11 (1H, d), 5.02-4.88 (2H, m), 4.66-4.42 (2H, m), 3.35-3.17 (1H, m), 2.98-2.89 (1H, m), 2.96 (3H, s), 2.84-2.78 (1H, m), 2.72-2.47 (1H, m),
 15 2.42-2.32 (1H, m), 2.14-1.58 (6H, m), 1.43 (9H, s).
 Anal. Calcd for C₃₃H₄₀N₄O₁₁S: C, 56.56; H, 5.75; N, 8.00. Found: C, 56.36; H, 5.82; N, 7.71. MS (ES⁺) 723 (56%), 718 (90), 701 (M⁺ + 1, 36), 645 (100).

[3S(1S,9S)] 3-[6,10-Dioxo-9-(methanesulphonylamino)-
 20 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(3-phenoxybenzoyloxy)pentanoic acid (505d), was
 synthesized by a similar method as compound 217 to afford a colourless foam (353mg, 73%): mp. 80-115°C;
 25 $[\alpha]_D^{23}$ -138° (c 0.11, MeOH); IR (KBr) 3327, 2937, 1728, 1666, 1584, 1529, 1487, 1443, 1413, 1328, 1273, 1227, 1189, 1155, 1134, 989, 754; ¹H NMR (D₆-DMSO) δ 8.82 (1H, d), 7.76-7.72 (1H, m), 7.61-7.53 (2H, m), 7.48-7.32 (4H, m), 7.24-7.17 (1H, m), 7.11-7.06 (2H, m),
 30 5.14-5.06 (3H, m), 4.73-4.64 (1H, m), 4.38-4.24 (2H, m), 2.92 (3H, s), 2.89-2.61 (3H, m), 2.38-2.27 (1H, m),

- 603 -

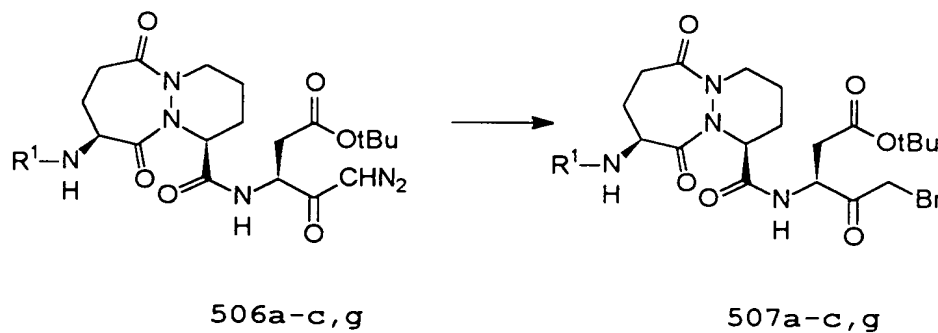
2.19-2.06 (2H, m), 2.02-1.79 (3H, m), 1.63-1.52 (1H, m). Anal. Calcd for $C_{29}H_{32}N_4O_{11}S \cdot 0.5H_2O$: C, 53.29; H, 5.09; N, 8.57; S, 4.90. Found: C, 53.24; H, 5.14; N, 8.34; S, 4.86. MS (ES^+) 643 (M - 1, 100%), 385 (62).

- 5 **[3S,4R(1S,9S)] t-Butyl 5-(3-chlorothien-2-oyloxy)-3-(6,10-dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-hydroxypentanoate (503e)**, was prepared by a similar method to that described for compound
- 10 **213e**, to afford an off white solid (70%): mp. 100-103°C; $[\alpha]_D^{25}$ -84.0° (c 0.05, CH_2Cl_2); IR (KBr) 3459-3359, 1722, 1664, 1514, 1368, 1328, 1278, 1247, 1155; 1H NMR ($CDCl_3$) δ 7.52 (1H, m), 7.06-6.99 (2H, m), 5.69 (1H, d, J = 9.0), 5.23 (1H, m), 4.61-4.16 (6H, m),
- 15 3.36-3.19 (1H, m), 2.96 (3H, s), 2.67-2.49, 2.42-2.32, 2.06-1.89, 1.69 (10H, 4m), 1.43 (9H, s).

- [3S(1S,9S)] t-Butyl 5-(3-chlorothien-2-oyloxy)-3-(6,10-dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoate (504e)**, was prepared by a similar method to that described for compound **216e**, to afford a white solid (98%): mp. 91-98°C; $[\alpha]_D^{25}$ -112.5° (c 0.06, CH_2Cl_2); IR (KBr) 3453-3364, 1727, 1668, 1513, 1420, 1368, 1245, 1155; 1H NMR ($CDCl_3$) δ 7.54
- 20 (1H, d, J = 5.3), 7.18 (1H, d, J = 7.18), 7.05 (1H, d, J = 5.4), 5.42 (1H, d, J = 8.9), 5.25 (1H, m), 5.02 (2H, m), 4.96-4.87 (1H, m), 4.65-4.42 (2H, m), 3.34-3.17 (1H, m), 2.97-2.93 (1H, m), 2.97 (3H, s), 2.87-2.78, 2.73-2.50, 2.38-2.32, 2.13-1.88, 1.69-1.60 (9H,
- 25 5m), 1.44 (9H, s).
- 30

- 604 -

[3*S*(1*S*,9*S*)] 5-(3-Chlorothien-2-oyloxy)-3-(6,10-dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-4-oxopentanoic acid (505e). A solution of 217 (0.33g, 0.51mmol) in dry dichloromethane (3ml) was cooled (ice/water) with protection from moisture. Trifluoroacetic acid (2ml) was added with stirring. The solution was kept at room temperature for 2h after removal of the cooling bath, then concentrated in vacuo. The residue was evaporated three times from dichloromethane, triturated with diethyl ether and filtered. The solid was purified by flash chromatography (silica gel, 0-6% methanol in dichloromethane) to give the product as a white glassy solid (0.296g, 98%): mp 110-122°C; $[\alpha]_D^{22}$ -163.5° (c 0.1, CH₃OH); IR (KBr) 3514-3337, 1726, 1664, 1513, 1420, 1245, 1152, 1134, 990; ¹H NMR (CD₃OD) δ 7.79 (1H, d, J = 5.2), 7.12 (1H, d, J = 5.2), 5.20 (1H, m), 5.02-4.72 (2H, m, masked by H₂O), 4.59-4.32 (3H, m), 3.48-3.29, 3.08-2.75, 2.50-2.41, 2.31-2.22, 2.08-1.89, 1.72-1.63 (11H, 6m), 2.95 (3H, s).



- 605 -

compound	R ¹
506a 507a	PhC(O) -
506b 507b	MeS(O) ₂ -
506c 507c	MeOC(O) -
506g 507g	CH ₃ C(O) -

5

10 [3*S*(1*S*,9*S*)] *t*-Butyl 3-(9-benzoylamino-6,10-dioxo-
 1,2,3,4,7,8,9,10-octahydro-6*H*-
 pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-5-diazo-
 4-oxopentanoate (506a). A solution of 212e (321mg,
 0.929mmol) and (3*S*) *t*-butyl 3-amino-5-diazo-4-
 15 oxopentanoate (198mg, 0.929mmol) in dichloromethane
 (3ml) was cooled to 0° and *N,N*-diisopropylethylamine
 (0.16ml, 1.86mmol) and [2-(1*H*-benzotriazol-1-yl)-
 1,1,3,3-tetramethyl-uronium tetrafluoroborate (328mg,
 1.02mmol) were added. The solution was stirred
 20 overnight at room temperature, diluted with ethyl
 acetate and washed with 1*M* NaHSO₄ (x2), aqueous NaHCO₃
 (x2), brine, dried over magnesium sulphate and
 evaporated. Chromatography on silica gel eluting with
 ethyl acetate gave 506a (425mg, 85%) as a colourless
 25 foam: [α]_D²³ -124.9° (c 0.2, CH₂Cl₂); IR (KBr) 3332,
 2111, 1728, 1658, 1532, 1421, 1392, 1367, 1279, 1256,
 1155; ¹H NMR (CDCl₃) δ 7.82 (2*H*, *m*), 7.49 (3*H*, *m*), 7.28
 (1*H*, *d*, *J* = 9.3), 7.05 (1*H*, *d*, *J* = 7.3), 5.06 (1*H*, *s*),
 5.18 (2*H*, *m*), 4.78 (1*H*, *m*), 4.62 (1*H*, *m*), 3.29 (1*H*, *m*),
 30 3.08-2.79 (3*H*, *m*), 2.58 (1*H*, *dd*, *J* = 16.8, 5.6), 2.20-

- 606 -

1.85 (4H, m), 1.70 (1H, m), 1.45 (9H, s). MS (ES⁺)
539.58 (M - 1, 97.9%) 529.59 (100).

[3S(1S,9S)] t-Butyl 5-diazo-3-[6,10-dioxo-(9-methanesulphonamido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoate (506b), was prepared by a similar method as compound 506a. 74% as yellow orange solid: mp. 75°C (decomp.); $[\alpha]_D^{20}$ -92.0° (c 0.036, CH₂Cl₂); IR (KBr) 3438, 2904, 2113, 1728, 1669, 1523, 1368, 1328, 1155; ¹H NMR (CDCl₃) δ 7.48 (1H, d, J = 8.1), 5.83-5.68 (1H, m), 5.55-5.50 (1H, m), 5.43-5.14 (1H, m), 4.83-4.45 (3H, m), 3.40-3.19 (1H, m), 2.98 (3H, s), 2.92-2.30 (4H, m), 2.24-1.70 (6H, m), 1.43 (9H, s).

[3S(1S,9S)] t-Butyl 5-diazo-3-[6,10-dioxo-(9-methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoate (506c), was prepared by a similar method as compound 506a to afford a pale yellow foam (405mg, 82%): $[\alpha]_D^{20}$ -144° (c 0.2, CH₂Cl₂); IR (KBr) 3339, 2978, 2958, 2112, 1728, 1674, 1530, 1459, 1415, 1367, 1274, 1252, 1154, 1063; ¹H NMR (CDCl₃) δ 7.23 (1H, d, J = 8.2), 5.51-5.31 (2H, m), 5.21-5.16 (1H, m), 4.77-4.55 (3H, m), 3.68 (3H, s), 3.35-3.18 (1H, m), 3.04-2.51 (4H, m), 2.40-2.30 (1H, m), 2.09-1.66 (5H, m), 1.45 (9H, s). MS (ES⁺) 493.

[3S(1S,9S)] t-Butyl 3-(9-acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-5-diazo-4-oxopentanoate (506g), was prepared by a similar

- 607 -

- method as compound **506a**. 81%: $[\alpha]_D^{28} -146.7^\circ$ (c 0.4, CH₂Cl₂); IR (KBr) 3438, 2904, 2113, 1728, 1669, 1523, 1368, 1328, 1155; ¹H NMR (CDCl₃) δ 7.32 (1H, d), 6.43 (1H, d), 5.50 (1H, s), 5.22 (1H, m), 4.94 (1H, m), 4.77 (1H, m), 4.60 (1H, m), 3.24 (1H, m), 3.03-2.52 (4H, m), 2.36 (1H, m), 2.10-1.64 (5H, m), 2.02 (3H, s), 1.45 (9H, s). Anal. Calcd for C₂₁H₂₀N₆O₇: C, 52.69; H, 6.32; N, 17.05. Found: C, 52.51; H, 6.27; N, 17.36. MS (ES⁺) 477 (M⁺ - 1, 100%).
- 10 **[3S(1S,9S)] t-Butyl 5-bromo-3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoate (507a)**. **506a** (3.0g, 5.55mmol) in dry dichloromethane (40ml) was cooled to 0° and 30%
 15 hydrobromic acid in acetic acid (1.1ml, 5.55mmol) was added dropwise over 4min. The mixture was stirred at 0° for 9min and quenched with aqueous sodium bicarbonate. The product was extracted into ethyl acetate, washed with aqueous sodium bicarbonate, brine,
 20 dried (MgSO₄) and evaporated to give 2.97g (92%) of a colourless foam: $[\alpha]_D^{23} -82.3^\circ$ (c 0.23, CH₂Cl₂); IR (KBr) 3333, 1726, 1659, 1530, 1458, 1447, 1422, 1395, 1368, 1279, 1256, 1222, 1155, 728; ¹H NMR (CDCl₃) δ 7.81 (2H, m), 7.50 (3H, m), 7.11 (1H, d, J = 8.0), 7.01 (1H, d, J = 7.4), 5.20 (2H, m), 5.00 (1H, m), 4.06 (2H, s), 3.28 (1H, m), 3.20-2.70 (4H, m), 2.42 (1H, m), 2.10-1.85 (4H, m), 1.72 (1H, m), 1.44 (9H, s). Anal. Calcd for C₂₆H₃₃N₄O₇Br•0.7H₂O: C, 51.53; H, 5.72; N, 9.24. Found: C, 51.55; H, 5.52; N, 9.09. MS (ES⁺) 595, 593
 30 (M⁺ + 1).

- 608 -

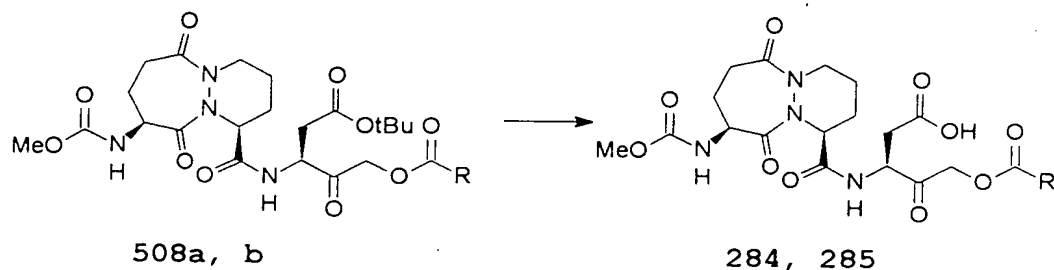
[3S(1S,9S)] t-Butyl 5-bromo-3-(6,10-dioxo-9-methanesulphonamido-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoate (507b), was prepared by a similar method
 5 as compound 507a. (68%) as an orange foam: $[\alpha]_D^{20}$ -135° (c 0.053, CH₂Cl₂); IR (KBr) 3429, 2944, 2935, 1723, 1670, 1458, 1408, 1327, 1225, 1154, 991; ¹H NMR (CDCl₃) δ 7.38 (1H, d, J = 8.2), 5.69 (1H, d, J = 9.3), 5.43-5.34 (1H, m), 5.07-4.97 (1H, m), 4.70-4.42 (2H, m), 4.12 (2H, s), 3.35-3.17 (1H, m), 3.10-2.69 (4H, m),
 10 2.98 (3H, s), 2.43-2.33 (1H, m), 2.15-1.65 (5H, m), 1.43 (9H, s). Anal. Calcd for C₂₀H₃₁BrN₄O₈S: C, 42.33; H, 5.51; N, 9.87. Found: C, 42.69; H, 5.52; N, 9.97.

[3S(1S,9S)] t-Butyl 5-bromo-3-(6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoate (507c), was prepared by a similar method
 15 as compound 507a to afford a pale yellow foam (320mg, 78%): $[\alpha]_D^{20}$ -107° (c 0.2, CH₂Cl₂); IR (KBr) 3401, 2956, 1726, 1670, 1528, 1452, 1415, 1395, 1368, 1276, 1251, 1155, 1064; ¹H NMR (CDCl₃) δ 7.07 (1H, d, J = 7.6), 5.47 (1H, d, J = 8.1), 5.21-5.16 (1H, m), 5.03-4.94 (1H, m), 4.75-4.56 (2H, m), 4.06 (2H, s), 3.69 (3H, s), 3.31-3.13 (1H, m), 3.03-2.92 (2H, m), 2.81-
 20 2.58 (2H, m), 2.41-2.31 (1H, m), 2.10-1.66 (5H, m), 1.44 (9H, s).

[3S(1S,9S)] t-Butyl 3-(9-acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-5-bromo-
 30 4-oxopentanoate (507g), was prepared by a similar

- 609 -

method as compound **507a** to afford a pale yellow foam (84%): $[\alpha]_D^{22}$ -109.6° (c 0.1, CH_2Cl_2); IR (KBr) 3324, 1727, 1659, 1535, 1458, 1444, 1423, 1369, 1279, 1256, 1223, 1155; ^1H NMR (CDCl_3) δ 7.12 (1H, d, $J = 7.8$), 6.33 (1H, d, $J = 7.5$), 5.19 (1H, m), 4.97 (2H, m), 4.58 (1H, m), 4.06 (2H, s), 3.20 (1H, m), 3.05-2.69 (4H, m), 2.35 (1H, m), 2.14-1.68 (5H, m), 2.03 (3H, s), 1.44 (9H, s). Anal. Calcd for $\text{C}_{21}\text{H}_{31}\text{BrN}_4\text{O}_7 \cdot 0.3\text{H}_2\text{O}$: C, 46.99; H, 5.93; N, 10.44. Found: C, 46.97; H, 5.90; N, 10.35.



10

compound	R
508a 284	
508b 285	

15 **[3S(1S,9S)] t-Butyl 5-(2,6-dichlorobenzoyloxy)-3-[6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoate (508a)**. To a solution of

- 610 -

506c (547mg, 1mmol) in DMF (4ml) was added potassium fluoride (145mg, 2.5mmol, 2.5 equiv). After 10min stirring at room temperature, 2,6-dichlorobenzoic acid (229mg, 1.2mmol, 1.2 equiv) was added. After 3h
 5 reaction at room temperature, ethyl acetate (30ml) was added. The solution was washed with a saturated solution of sodium bicarbonate (30ml), brine, dried over MgSO₄ and concentrated in vacuo to afford 590mg (90%) of a pale yellow foam: $[\alpha]_D^{22} -85^\circ$ (c 0.20, CH₂Cl₂); IR (KBr) 3400, 2956, 1737, 1675, 1528, 1434, 1414, 1368, 1344, 1272, 1197, 1152, 1061; ¹H NMR (CDCl₃) δ 7.36-7.33 (3H, m), 7.04 (1H, d, J = 8.0), 5.46 (1H, d, J = 7.8), 5.19-5.16 (1H, m), 5.08 (2H, AB), 4.97 - 4.55 (1H, m), 4.69-4.55 (2H, m), 3.68 (3H, s),
 10 3.30-3.10 (1H, m), 3.01-2.50 (4H, m), 2.40-2.33 (1H, m), 2.15-1.60 (5H, m), 1.44 (9H, s). Anal. Calcd for C₂₈H₃₄Cl₂N₄O₁₀: C, 51.15; H, 5.21; N, 8.52. Found: C, 51.35; H, 5.32; N, 8.56.

[3S(1S,9S)] 5-(2,6-Dichlorobenzoyloxy)-3-[6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoic acid (284), was synthesized from 508a via method used to prepare 505 from 504 which afforded 330mg (65%) of a white solid: mp. 115°C (decomp.);
 25 $[\alpha]_D^{20} -107^\circ$ (c 0.2, CH₂Cl₂); IR (KBr) 3340, 2954, 1738, 1664, 1530, 1434, 1272, 1198, 1148, 1060; ¹H NMR (D₆-DMSO) δ 8.91 (1H, d, J = 7.2H), 7.67-7.63 (3H, m), 7.54 (1H, d, J = 8.0), 5.24 (2H, s), 5.20-5.15 (1H, m), 4.79-4.70 (1H, m), 4.46-4.37 (2H, m), 3.58 (3H, s),
 30 3.33-3.20 (1H, m), 2.94-2.55 (4H, m), 2.30-1.60 (6H,

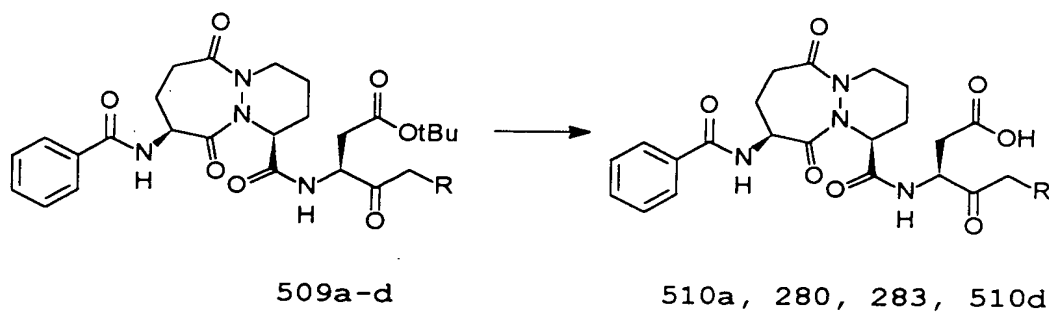
- 611 -

m). Anal. Calcd for $C_{24}H_{26}Cl_2N_4O_{10} \cdot H_2O$: C, 46.54; H, 4.56; N, 9.05. Found: C, 46.36; H, 4.14; N, 8.88.

[3S(1S,9S)] t-Butyl 5-(2,6-dimethylbenzoyloxy)-3-[6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-
 5 octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoate (508b), was synthesized by a similar method as compound 508a to afford a pale yellow foam (460mg, 82%): $[\alpha]_D^{22} -115^\circ$ (c 0.20, CH_2Cl_2); IR (KBr) 3413, 2960, 1729, 1675, 1528, 1514, 1461,
 10 1421, 1368, 1265, 1116, 1096; 1H NMR ($CDCl_3$) δ 7.27-7.03 (4H, m), 5.48 (1H, d, $J = 8.2$), 5.20-5.14 (1H, m), 5.04 (2H, AB), 4.93-4.86 (1H, m), 4.80-4.56 (2H, m), 3.77 (3H, s), 3.32-3.15 (1H, m), 3.00-2.56 (4H, m), 2.37 (6H, s), 2.19-1.77 (5H, m), 1.45 (9H, s), 2.41-2.25
 15 (1H, m). MS (ES^+) 617.

[3S(1S,9S)] 5-(2,6-Dimethylbenzoyloxy)3-[6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoic acid (285), was synthesized by a similar
 20 method as compound 284 to afford a white solid (303mg, 78%): mp. $110^\circ C$ (decomp.); $[\alpha]_D^{20} -128^\circ$ (c 0.10, CH_2Cl_2); IR (KBr) 3339, 2958, 1731, 1666, 1529, 1420, 1266, 1248, 1115, 1070; 1H NMR (D_6 -DMSO) δ 8.90 (1H, d, $J = 7.4$), 7.54 (1H, d, $J = 7.9$), 7.36-7.28 (1H, m),
 25 7.17-7.14 (2H, m), 5.19-5.15 (3H, m), 4.84-4.74 (1H, m), 4.45-4.37 (2H, m), 3.59 (3H, s), 3.45-3.25 (1H, m), 2.95-2.64 (4H, m), 2.35 (6H, s), 2.30-1.60 (6H, m).
 Anal. Calcd for $C_{26}H_{32}N_4O_{10} \cdot H_2O$: C, 53.98; H, 5.92; N, 9.68. Found: C, 53.50; H, 5.52; N, 9.49. MS (ES^+)
 30 559.

- 612 -



compound	R
509a 510a	
509b 280	
509c 283	
509d 510d	

[3S(1S,9S)] 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-5-(2-mercaptothiazole)-4-oxopentanoic acid (510a). A

15 solution of 506a (2.27g, 4.2mmol) in dry dichloromethane (50ml) was treated with 30% hydrobromic

- 613 -

acid in acetic acid (1.84ml, 9.2mmol, 2.2equiv) at 0°C, under nitrogen. After 10min stirring at 0°C the reaction was complete and a white solid crystallised in the medium. The solid was filtered and washed with ethylacetate and diethylether to afford 2.20g (100%) of [3S(1S,9S)] 5-bromo-3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoic acid which was used without further purification: ¹H NMR (D₆-DMSO) δ 8.87 (1H, d, J = 7.3), 8.63 (1H, d, J = 7.6), 7.91-7.87 (2H, m), 7.60-7.44 (3H, m), 6.92 (1H, bs), 5.14-5.09 (1H, m), 4.92-4.65 (2H, m), 4.43 (2H, AB), 4.41-4.35 (1H, m), 3.33-3.22 (1H, m), 2.98-2.90 (1H, m), 2.89-2.57 (2H, m), 2.35-2.15 (3H, m), 1.99-1.91 (2H, m), 1.75-1.60 (2H, m). A solution of the bromoketone (535mg, 1mmol) in dry DMF (10ml) was treated with potassium fluoride (150mg, 2.5mmol, 2.5 equiv), under nitrogen. After 5min stirring at room temperature, 2-mercaptothiazole (140mg, 1.2mmol, 1.2equiv) was added. After overnight reaction ethylacetate (150ml) was added and the organic solution was washed with brine, dried over magnesium sulphate and reduced in vacuo. The residue was crystallised in diethyl ether, filtered and purified on silica gel using a gradient of MeOH (0% to 5%) in dichloromethane. Evaporation afforded 344mg (60%) of a white solid: mp. 90-95°C (decomp.); [α]_D²⁰ -82° (c 0.2, CH₂Cl₂); IR (KBr) 3328, 2941, 1745, 1659, 1535, 1422, 1276, 1255, 1223, 1072; ¹H NMR (D₆-DMSO) δ 8.92 (1H, d, J = 7.6), 8.68 (1H, d, J = 7.6), 7.98-7.90 (2H, m), 7.75-7.67 (1H, m), 7.64-7.50 (4H, m), 5.22-5.18 (1H, m), 4.95-4.74 (2H, m), 4.58-4.38 (3H, m), 3.52-3.19 (1H, m), 3.05-2.65 (4H, m), 2.40-1.50 (6H, m). Anal.

- 614 -

Calcd for $C_{25}H_{27}N_5O_4S_2 \cdot H_2O$: C, 50.75; H, 4.94 N, 11.84.
 Found: C, 51.34; H, 4.70; N, 11.58. MS (ES^+) 572.

[3*S*(1*S*,9*S*)] *t*-Butyl 3-(9-benzoylamino-6,10-dioxo-
 1,2,3,4,7,8,9,10-octahydro-6*H*-

- 5 pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-4-oxo-5-
 (1-phenyl-1*H*-tetrazole-5-thio) pentanoate (509*b*). 507*a*
 (100mg, 0.17mmol) in dry dimethylformamide (1.5ml) was
 treated with 1-phenyl-1*H*-tetrazole-5-thiol (33mg,
 0.187mmol) and potassium fluoride (15mg, 0.34mmol).
 10 The mixture was stirred at room temperature for 2h,
 diluted with ethyl acetate, washed with aqueous sodium
 bicarbonate (x2), brine, dried ($MgSO_4$) and evaporated.
 The product was purified by flash chromatography on
 silica gel eluting with ethyl acetate to give 103mg
 15 (88%) as a colourless foam: $[\alpha]_D^{23} -92.2^\circ$ (c 0.1,
 CH_2Cl_2); IR (KBr) 3334, 1726, 1660, 1528, 1501, 1417,
 1394, 1368, 1279, 1253, 1155; 1H NMR ($CDCl_3$) δ 7.82 (2*H*,
m), 7.60-7.40 (8*H*, *m*), 7.39 (1*H*, *d*, $J = 8.1$), 7.05 (1*H*,
d, $J = 7.3$), 5.26 (1*H*, *m*), 5.15 (1*H*, *m*), 4.99 (1*H*, *m*),
 20 4.60 (2*H*, *m*), 4.30 (1*H*, *d*, $J = 17.2$), 3.32 (1*H*, *m*),
 3.10-2.75 (4*H*, *m*), 2.40 (1*H*, *m*), 2.24 (1*H*, *m*), 1.90
 (3*H*, *m*), 1.75 (1*H*, *m*), 1.44 (9*H*, *s*). MS (ES^+) 691.47
 ($M^+ + 1$).

[3*S*(1*S*,9*S*)] 3-(9-Benzoylamino-6,10-dioxo-

- 25 1,2,3,4,7,8,9,10-octahydro-6*H*-
 pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-4-oxo-
 5(1-phenyl-1*H*-tetrazole-5-thio) pentanoic acid (280),
 was synthesized via method used to prepare 505 from
 504. 509*b* (98mg, 0.142mmol) in dichloromethane (1ml)
 30 was cooled to 0° and trifluoroacetic acid (1ml) was
 added. The mixture was stirred at 0° for 15min and at

- 615 -

room temperature for 30min before evaporation under reduced pressure. The residue was triturated with dry toluene and evaporated. Chromatography on silica gel eluting with 10% methanol in dichloromethane gave a
 5 colourless glass which was crystallised from dichloromethane/diethyl ether to give 62mg (69%) of colourless solid: mp. 145°C (decomp.); $[\alpha]_D^{22}$ -80.9° (c 0.1, CH₂Cl₂); IR (KBr) 3400, 1727, 1658, 1530, 1501, 1460, 1445, 1416, 1280, 1254; ¹H NMR (CDCl₃) δ 8.00 (1H,
 10 m), 7.79 (2H, d, J = 6.7), 7.58-7.30 (9H, m), 5.25 (2H, m), 4.94 (1H, m), 4.53 (2H, m), 4.35 (1H, m), 3.35 (1H, m), 3.01 (3H, m), 2.73 (1H, m), 2.38 (1H, m), 1.98 (4H, m), 1.64 (1H, m). Anal. Calcd for C₂₉H₃₀N₈O₇S•0.2TFA: C, 53.71; H, 4.63 N, 17.04. Found: C, 53.97; H, 4.92; N,
 15 16.77. MS (ES⁺) 633.55 (M⁺ - 1).

[3S(1S,9S)] t-Butyl 3-[9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(3-pyridyloxy)pentanoate (509c), was prepared by a
 20 similar method as compound 509b to afford a colourless glass (34%): $[\alpha]_D^{22}$ -77.1° (c 0.25, CH₂Cl₂); IR (film) 3311, 1724, 1658, 1603, 1578, 1536, 1488, 1458, 1426, 1368, 1340, 1279, 1256, 1231, 1155, 707; ¹H NMR (CDCl₃) δ 8.29 (2H, m), 7.84 (2H, m), 7.48 (4H, m), 7.22 (3H,
 25 m), 5.20 (2H, m), 4.90 (2H, m), 4.58 (1H, m), 3.29 (1H, m), 3.20-2.70 (4H, m), 2.38 (2H, m), 1.96 (4H, m), 1.68 (1H, m), 1.42 (9H, s). MS (ES⁺) 608.54 (M + 1).

[3S(1S,9S)] 3-[9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-
 30

- 616 -

(3-pyridyloxy)pentanoic acid (283), was prepared by a similar method as compound 280 to afford a colourless foam (100%): mp. ~125°C; $[\alpha]_D^{19}$ -84.1° (c 0.1, 20% MeOH/CH₂Cl₂); IR (KBr) 3401, 1736, 1663, 1538, 1489, 1459, 1425, 1281, 1258, 1200, 1134; ¹H NMR (CD₃OD/CDCl₃) δ 8.38 (2H, m), 7.84-7.40 (8H, m), 5.16 (4H, m), 4.80 (1H, m), 4.56 (1H, m), 3.50 (1H, m), 3.12 (2H, m), 2.82 (2H, m), 2.37 (1H, m), 2.10-1.65 (5H, m). Anal. Calcd for C₂₇H₂₉N₅O₈•0.4H₂O: C, 51.77; H, 4.61; N, 10.41.
 10 Found: C, 52.19; H, 4.93; N, 9.99.

[3S(1S,9S)] t-Butyl 3-[6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-9-(phenylcarbonylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-{2-[4(3H)-pyrimidone]}pentanoate (509d), was
 15 synthesized by a similar method as compound 509b to afford a colourless solid (49.6mg, 82%): ¹H NMR (CDCl₃) δ 8.02 (1H, s), 7.95-7.86 (1H, m), 7.84-7.76 (2H, m), 7.62-7.35 (4H, m), 7.22-7.07 (1H, m), 6.43 (1H, d), 5.26-5.08 (2H, m), 5.03-4.72 (3H, m), 4.66-4.50 (1H, m), 3.43-3.19 (1H, m), 3.15-2.97 (1H, m), 2.86-2.72 (3H, m), 2.48-2.31 (1H, m), 2.18-1.60 (6H, m), 1.43 (9H, s).
 20

[3S(1S,9S)] 3-[6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-9-(phenylcarbonylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-{2-[4(3H)-pyrimidone]}pentanoic acid (510d), was
 25 synthesized by a similar method as compound 280 to afford a colourless solid (25.7mg, 57%): mp. 140-80°C; IR (KBr) 3391, 2945, 1733, 1664, 1530, 1422, 1363, 1277, 1259, 1204; ¹H NMR (CD₃OD) δ 8.23 (1H, s), 7.94
 30

10

- 618 -

- (methylsulphonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoic acid (505f), was prepared by a similar method as compound 508a using 507b and 3-chloro-2-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one and directly followed by the hydrolysis of 504f with trifluoroacetic to afford a tan powder (65mg, 30%): $[\alpha]_D^{20}$ -128° (c 0.10, MeOH); IR (KBr) 3414, 2928, 1667, 1527, 2459, 1407, 1328, 1274, 1153, 1134; ^1H NMR (MeOD) δ 9.35 (1H, d, J = 6.6H), 8.34 (1H, t, J = 7.2H), 7.99-7.95 (1H, m), 7.76-7.69 (1H, m), 5.85-5.45 (3H, m), 5.30-5.21 (1H, m), 4.93-4.66 (2H, m), 3.81-3.65 (1H, m), 3.66 (3H, m), 3.45-2.52 (4H, m), 2.52-1.71 (6H, m). D.J. Hlasta et al., J. Med. Chem. 1995, 38, 4687-4692.
- 15 [3S(1S,9S)] t-Butyl 3-(6,10-dioxo-9-methanesulphonamido-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5(1-phenyl-1H-tetrazole-5-thio)pentanoate (504g), was prepared by a similar method as compound 509b, (83%) as a colourless foam: $[\alpha]_D^{23}$ -112.7° (c 0.2, CH_2Cl_2); IR (KBr) 3312, 1726, 1668, 1501, 1413, 1395, 1369, 1328, 1276, 1254, 1155; ^1H NMR (CDCl_3) δ 7.59 (5H, m), 7.48 (1H, d, J = 8.0), 5.68 (1H, d, J = 9.0), 5.37 (1H, m), 4.95 (1H, m), 4.62-4.31 (4H, m), 3.36 (1H, m), 2.98 (3H, s), 2.88 (4H, m), 2.66 (1H, m), 2.42 (2H, m), 1.98 (1H, m), 1.75 (1H, m), 1.43 (9H, s).
- 25

- [3S(1S,9S)] 3-(6,10-Dioxo-9-methanesulphonamido-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5(1-phenyl-1H-tetrazole-5-thio)pentanoic acid (280b),
- 30

- 619 -

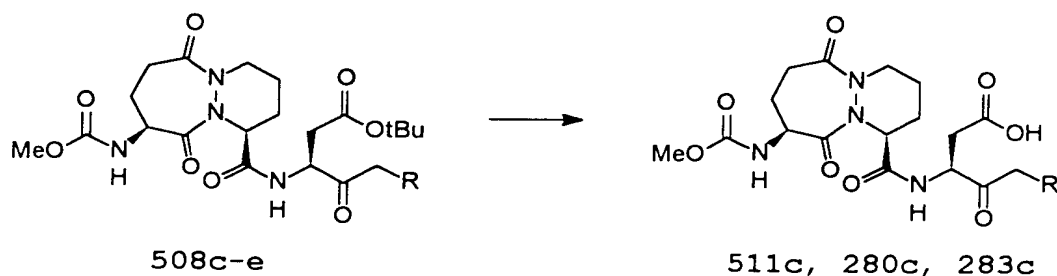
was prepared by a similar method as compound **280**,
 (100%) as a colourless foam: mp. 120-5°C; $[\alpha]_D^{25}$ -
 112.4° (c 0.1, CH₂Cl₂); IR (KBr) 3328, 1730, 1664,
 1529, 1501, 1410, 1328, 1277, 1219, 1153, 1134, 991; ¹H
 5 NMR (CDCl₃) δ 8.07 (1H, d, J = 7.8), 7.58 (5H, s), 6.41
 (1H, d, J = 9.5), 5.32 (1H, m), 5.04 (1H, m), 4.70 (1H,
 d, J = 17.5), 4.60 (3H, m), 3.50-2.9 (3H, m), 2.98 (3H,
 s), 2.45 (2H, m), 2.06 (4H, m), 1.68 (1H, m).

[3S(1S,9S)] t-Butyl 3-(6,10-dioxo-9-
 10 **methanesulphonamido-1,2,3,4,7,8,9,10-octahydro-6H-**
pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-
5(3-pyridyloxy)pentanoate (504h), was prepared by a
 similar method as compound **509b** (24%) as a colourless
 foam: $[\alpha]_D^{23}$ -101.0° (c 0.2, CH₂Cl₂); IR (KBr) 3330,
 15 1727, 1669, 1425, 1396, 1369, 1328, 1276, 1256, 1231,
 1155, 1137, 991; ¹H NMR (CDCl₃) δ 8.28 (2H, br d, J =
 9.4), 7.71 (1H, d, J = 7.9), 7.22 (2H, s), 6.03 (1H, d,
 J = 9.4), 5.36 (1H, m), 4.95 (2H, m), 4.52 (2H, m),
 3.29 (1H, m), 3.07 (3H, s), 3.23-2.75 (3H, m), 2.66-
 20 2.35 (2H, m), 2.30-1.60 (5H, m), 1.42 (9H, s).

[3S(1S,9S)] 3-(6,10-Dioxo-9-methanesulphonamido-
1,2,3,4,7,8,9,10-octahydro-6H-
pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-
5(3-pyridyloxy)pentanoic acid (283b), was prepared by a
 25 similar method as compound **280**, (100%) as a colourless
 foam: mp. 120-5°C ; $[\alpha]_D^{25}$ -85.2° (c 0.1, 10%
 CH₃OH/CH₂Cl₂); IR (KBr) 3337, 1738, 1667, 1560, 1457,
 1424, 1326, 1317, 1278, 1258, 1200, 1189, 1150, 1133,
 991; ¹H NMR (CDCl₃/CD₃OD) δ 8.35 (2H, m), 7.54 (2H, m),

- 620 -

5.32 (2H, m), 4.83 (2H, m), 4.45 (2H, m), 3.43-2.77 (4H, m), 2.97 (3H, s), 2.42 (2H, m), 2.05-1.72 (5H, m).



5

compound	R
508c 511c	
508d 280c	
508e 283c	

10

[3*S*(1*S*,9*S*)] *t*-Butyl 3-[6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-5-(2-mercaptopyrimidine)-4-oxo-pentanoate (508c), was prepared by a similar method as compound 509b to afford 544mg (97%) of a pale yellow foam: $[\alpha]_D^{20}$ -86° (c 0.19, CH₂Cl₂); IR (KBr) 3426, 2947, 1725, 1669, 1551, 1418,

- 621 -

1383, 1253, 1155, 1064; ^1H NMR (CDCl_3) δ 8.49 (2H, d, J = 4.8), 7.13 (1H, d, J = 7.9), 7.03-6.98 (1H, m), 5.47 (1H, d, J = 7.9), 5.23-5.19 (1H, m), 5.09-5.01 (1H, m), 4.84-4.51 (2H, m), 4.04 (2H, AB), 3.69 (3H, s), 3.38-
 5 3.19 (1H, m), 3.06-2.64 (4H, m), 2.40-1.76 (6H, m), 1.43 (9H, s). Anal. Calcd for $\text{C}_{25}\text{H}_{34}\text{N}_6\text{O}_8\text{S}$: C, 51.89; H, 5.92; N, 14.52. Found: C, 51.49; H, 6.04; N, 13.87. MS (ES^+) 579.

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-9-(methoxycarbonyl)-amino-
 10 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido]-5-(2-mercaptopyrimidine)-4-oxopentanoic acid (511c), was prepared by a similar method as compound 280 to afford 370mg (79%) of a white powder: mp. 105°C (dec); $[\alpha]_{\text{D}}^{22}$
 15 -94° (c 0.20, CH_2Cl_2); IR (KBr) 3316, 3057, 2957, 1724, 1664, 1252, 1416, 1384, 1254, 1189, 1063; ^1H NMR (D_6 -DMSO) δ 8.85 (1H, d, J = 7.8), 8.62 (2H, d, J = 4.7), 7.53 (1H, d, J = 8.0), 7.28-7.23 (1H, m), 5.21-5.17 (1H, m), 4.87-4.79 (1H, m), 4.47-4.35 (2H, m), 4.23
 20 (2H, AB), 3.58 (3H, s), 3.30-3.21 (1H, m), 2.95-2.50 (4H, m), 2.35-1.60 (6H, m). Anal. Calcd for $\text{C}_{21}\text{H}_{26}\text{N}_6\text{O}_8\text{S} \cdot \text{H}_2\text{O}$: C, 46.66; H, 5.22; N, 15.55. Found: C, 46.66; H, 5.13; N, 15.07. MS (ES^+) 523, (ES^+) 521.

[3*S*(1*S*,9*S*)] *t*-Butyl 3-[6,10-dioxo-9-
 25 (methoxycarbonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido]-4-oxo-5-[5-(1-phenyltetrazolyl)-thio]pentanoate (508d), was synthesized by a similar method as compound 509b to afford a colourless solid (269mg, 87%): mp. 80-110°C;
 30 $[\alpha]_{\text{D}}^{23}$ -108° (c 0.60 CH_2Cl_2); IR (KBr) 3315, 2977, 1727,

- 622 -

1688, 1527, 1501, 1458, 1418, 1368, 1279, 1250, 1155, 1064; ^1H NMR (CDCl_3) δ 7.70 (1H, d), 7.63-7.53 (5H, m), 5.84 (1H, d), 5.34-5.27 (1H, m), 5.05-4.92 (1H, m), 4.78-4.54 (3H, m), 4.38 (1H, d), 3.66 (3H, s), 3.37-
 5 3.19 (1H, m), 3.07-2.94 (1H, m), 2.91-2.82 (2H, m), 2.71-2.56 (1H, m), 2.40-2.30 (1H, m), 2.19-2.13 (1H, m), 2.08-1.68 (4H, m), 1.42 (9H, s). MS (ES^+) 667 (31%), 645 ($\text{M}^+ + 1$, 100), 589 (62).

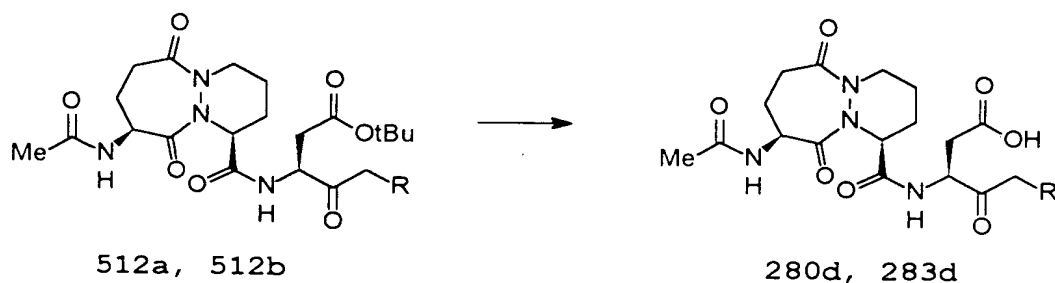
[3S(1S,9S)] 3-[6,10-Dioxo-9-(methoxycarbonylamino)-
 10 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-[5-(1-phenyltetrazolyl)-thio]pentanoic acid (280c), was synthesized by a similar method as compound 280 to afford a pale cream solid (203mg, 88%): mp. 105-130°C;
 15 $[\alpha]_D^{22}$ -235° (c 0.11 MeOH); IR (KBr) 3342, 2951, 1727, 1667, 1529, 1501, 1459, 1416, 1276, 1252, 1225, 1192, 1062; ^1H NMR (D_6 -DMSO) δ 8.89 (1H, d), 7.69 (5H, s), 7.50 (1H, d), 5.18-5.11 (1H, m), 4.79-4.69 (1H, m), 4.57 (2H, s), 4.42-4.32 (1H, m), 3.54 (3H, s), 2.92-
 20 2.63 (3H, m), 2.21-1.82 (5H, m), 1.65-1.57 (1H, m). MS (ES^+) 587 ($\text{M} - 1$, 100%).

[3S(1S,9S)] t-Butyl 3-[6,10-dioxo-9-(methoxycarbonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-
 25 (3-pyridinyloxy) pentanoate (508e), was synthesized by a similar method as compound 509b to afford a pale orange solid (199mg, 25%): mp. 80-120°C; $[\alpha]_D^{23}$ -89° (c 0.51 CH_2Cl_2); IR (KBr) 3333, 2978, 1726, 1669, 1578, 1536, 1478, 1426, 1368, 1277, 1253, 1232, 1155, 1064;
 30 ^1H NMR (CDCl_3) δ 8.41-8.18 (2H, m), 7.81 (1H, d), 7.26-

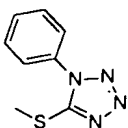
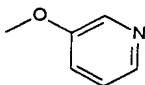
- 623 -

7.20 (2H, s), 5.91 (1H, d), 5.24-5.16 (1H, m), 5.07-4.86 (3H, m), 4.81-4.51 (2H, m), 3.67 (3H, s), 3.34-3.16 (1H, m), 3.10-2.81 (3H, m), 2.72-2.54 (1H, m), 2.41-2.31 (1H, m), 2.07-1.62 (5H, m), 1.47 (9H s). MS (ES⁺) 562 (M⁺ + 1, 100%), 506 (38).

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-9-(methoxycarbonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido]-4-oxo-5-(3-pyridinyloxy)pentanoic acid (283c), was synthesized by a similar method as compound 280 to afford an off-white powder (167mg, 98%): mp. 90-105°C; [α]_D²² -106° (c 0.11 MeOH); IR (KBr) 3325, 3070, 2956, 1669, 1544, 1423, 1256, 1199, 1133, 1062; ¹H NMR (D₆-DMSO) δ 8.95 (1H, d), 8.45-8.20 (2H, m), 7.53-7.45 (3H, m), 5.19-5.08 (3H, m), 4.70-4.62 (1H, m), 4.41-4.30 (2H, m), 3.53 (3H, s), 2.92-2.68 (3H, m), 2.22-2.06 (2H, m), 1.95-1.82 (2H, m), 1.63-1.53 (1H, m). MS (ES⁺) 506 (M⁺ + 1, 100%).



- 624 -

compound	R
512a 280d	
512b 283d	

5

[3*S*(1*S*,9*S*)] *t*-Butyl 3-(9-acetamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-4-oxo-5-(1-phenyl-1*H*-tetrazole-5-thio)pentanoate (512a), was
 10 prepared by a similar method as compound 509b, to afford (83%) as a colourless foam: $[\alpha]_D^{23}$ -129.6° (c 0.1, CH₂Cl₂); IR (KBr) 3323, 1726, 1664, 1531, 1501, 1444, 1415, 1394, 1369, 1279, 1254, 1156; ¹H NMR (CDCl₃) δ 7.59 (5*H*, s), 7.37 (1*H*, d, *J* = 7.9), 6.38 (1*H*,
 15 d, *J* = 7.4), 5.27 (1*H*, m), 4.98 (2*H*, m), 4.58 (2*H*, d + m), 4.28 (1*H*, d, *J* = 17.2), 3.28 (1*H*, m), 3.10-2.65 (4*H*, m), 2.31 (2*H*, m), 2.03 (3*H*, s), 2.10-1.72 (4*H*, m), 1.48 (9*H*, s).

[3*S*(1*S*,9*S*)] 3-(9-Acetamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-4-oxo-5-(1-phenyl-1*H*-tetrazole-5-thio)pentanoic acid (280d), was prepared by a similar
 20 method as compound 280, to afford (77%) as a colourless foam: $[\alpha]_D^{22}$ -93.3° (c 0.1, CH₂Cl₂); IR (KBr) 3316,

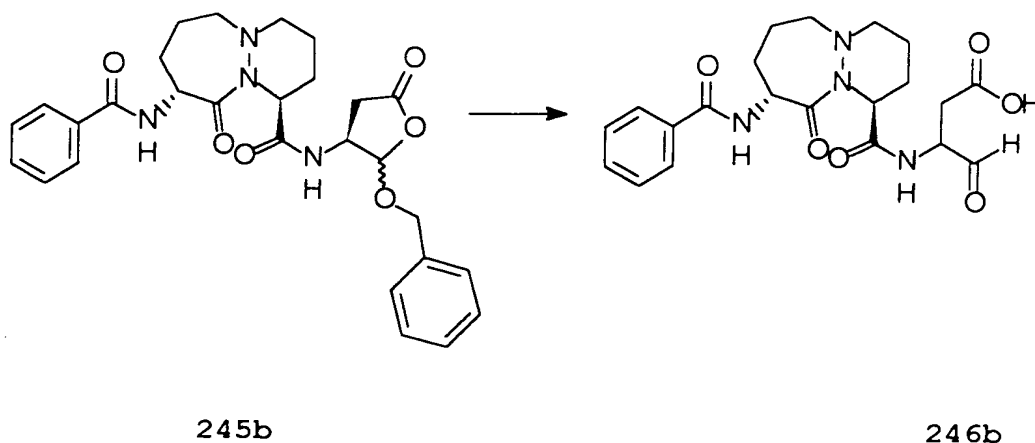
- 625 -

1728, 1659, 1531, 1501, 1415, 1341, 1278, 1253, 1222, 1185; ^1H NMR (CDCl_3) δ 8.05 (1H, d, $J = 7.9$), 7.57 (5H, br s), 5.30 (1H, m), 5.01 (2H, m), 4.70-4.10 (4H, m), 3.40-2.85 (4H, m), 2.62 (1H, m), 2.33 (1H, m), 2.27-
 5 1.65 (5H, m), 2.01 (3H, s).

[3S(1S,9S)] t-Butyl 3-(9-acetamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5-(3-pyridyloxy)pentanoate (512b), was prepared by a
 10 similar method as compound **509b**, to afford (9%) as a colourless foam: IR (KBr) 3333, 1727, 1661, 1542, 1427, 1369, 1279, 1257, 1232, 1156; ^1H NMR (CDCl_3) δ 8.30 (2H, m), 7.20 (3H, m), 6.45 (1H, d, $J = 7.4$), 5.17 (1H, m), 4.91 (3H, m), 4.55 (1H, m), 3.27 (1H, m), 3.14-2.70
 15 (4H, m), 2.41 (1H, m), 2.04 (3H, s), 2.10-1.65 (6H, m), 1.44 (9H, s).

[3S(1S,9S)] 3-(9-Acetamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5-(3-pyridyloxy)pentanoic acid (283d), was prepared by a similar method as compound
 20 **280**. (100%) as a colourless foam: $[\alpha]_D^{22} -106.0^\circ$ (c 0.2, 10% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$); IR (KBr) 3312, 1735, 1664, 1549, 1426, 1279, 1258, 1200, 1135; ^1H NMR (CDCl_3) δ 8.27 (2H, m), 7.46 (2H, m), 5.09 (1H, m), 4.79 (3H, m), 4.47 (1H, m), 3.40 (1H, m), 3.30-2.70 (3H, m), 2.54 (1H, m), 2.30
 25 (1H, m), 1.98 (3H, s), 2.05-1.65 (4H, m).

- 626 -



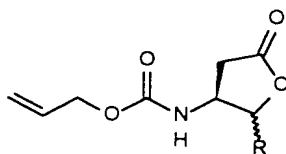
[1*S*,9*R*(2*RS*,3*S*)] 9-Benzoylamino-*N*-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-1,2,3,4,7,8,9,10-octahydro-10-oxo-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide (245b), was prepared from (1*S*,9*R*) 9-Benzoylamino-1,2,3,4,7,8,9,10-octahydro-10-oxo-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxylic acid by the method described for **245** to afford 416mg (85%) of a colourless foam (~1:1 mixture of diastereoisomers): IR (KBr) 3392, 3302, 2942, 1792, 1642, 1529, 1520, 1454, 1119; ¹H NMR (CDCl₃) δ 7.79 (2H, m), 7.51-7.09 (10H, m), 5.52 (0.5H, d, *J* = 5.3), 5.51 (0.5H, s), 5.36 (1H, m), 4.84 (1H, m), 4.74-4.59 (1.5H, m), 4.51 (1H, m), 4.38 (0.5H, m), 3.22-2.83 (5H, m), 2.51 (1H, m), 2.25 (2H, m), 2.01-1.46 (6H, m). Anal. Calcd for C₂₈H₃₂N₄O₆•0.75H₂O: C, 62.97; H, 6.32; N, 10.49. Found: C, 63.10; H, 6.16; N, 10.21. MS (ES⁺) 521 (*M* + 1, 100%).

[3*S*(1*S*,9*R*)] 3-(9-Benzoylamino-1,2,3,4,7,8,9,10-octahydro-10-oxo-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (246b), was prepared from **245b** by the method described for **246** to afford

- 627 -

104mg (33%) of a white powder: mp. 115-119°C; $[\alpha]_D^{24}$ - 19.8° (c 0.2 MeOH); IR (KBr) 3293, 2944, 1786, 1639, 1578, 1537, 1489, 1450, 1329, 1162, 1124; ^1H NMR (CD_3OD) δ 7.85 (2H, d, $J = 7.0$), 7.49 (3H, m), 5.49 (1H, m), 4.55 (1H, m), 4.30 (2H, m), 3.40 (1H, m), 3.19-2.89 (3H, m), 2.63 (2H, m), 2.16-1.81 (5H, m), 1.60 (3H, m). Anal. Calcd for $\text{C}_{21}\text{H}_{26}\text{N}_4\text{O}_6 \cdot \text{H}_2\text{O}$: C, 56.24; H, 6.29; N, 12.49. Found: C, 56.54; H, 6.05; N, 12.29. MS (ES^+) 429 ($\text{M} - 1$, 100%).


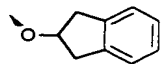
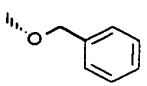
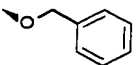



10 Compounds **513a-j** were prepared as described below.

**513a-f**

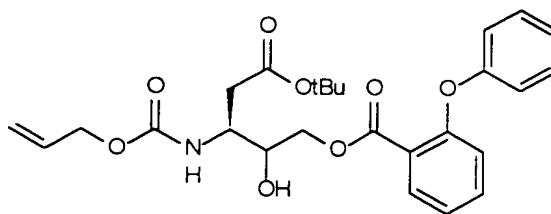
15

compound	R
513a	
513a-1	
513a-2	
513b	
513b-1	

- 628 -

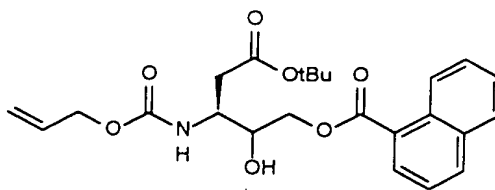
513b-2	
513c	
513d	
513e	
513f	
513f-1	
513f-2	

5

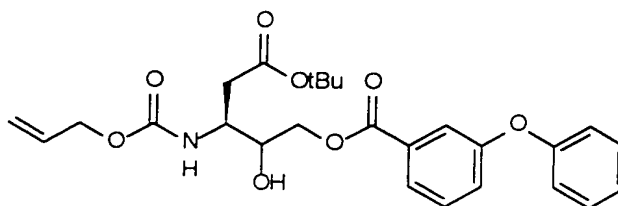


513g

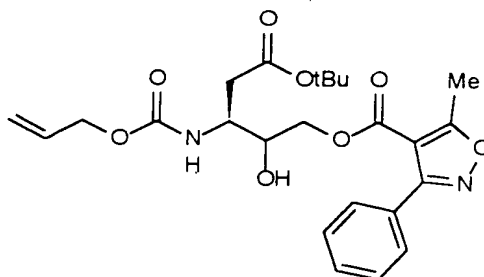
- 629 -



513h



513i



513j

(2*RS*,3*S*) 3-(Allyloxycarbonyl)amino-2-(2-phenethyloxy)-
 5-oxotetrahydrofuran (513a), was prepared by a similar
 method as compound 513d/e to afford a mixture of
 diastereoisomers (670mg, 50%) as an oil: IR (KBr) 3331,
 2946, 1790, 1723, 1713, 1531, 1329, 1257, 1164, 1120,
 1060, 977, 937, 701; ¹H NMR (CDCl₃) δ 7.36-7.18 (5H, m),
 5.99-5.83 (1H, m), 5.41-5.34 (2H, m), 5.28-5.18 (2H,

- 630 -

m), 4.59-4.56 (2H, m), 4.32-3.96 (2H, m), 3.85-3.73 (1H, m), 3.02-2.76 (3H, m), 2.49-2.34 (1H, m).

(2*RS*,3*S*) 3-(Allyloxycarbonyl)amino-2-cyclopentyloxy-5-oxotetrahydrofuran (513b), was prepared as 513d/e to afford 8g (51%) of a mixture of diastereoisomers as a clear oil: $[\alpha]_D^{20} -13^\circ$ (c 0.25, CH₂Cl₂); IR (KBr) 3325, 2959, 2875, 1790, 1723, 1535, 1420, 1328, 1257, 1120, 1049, 973, 937; ¹H NMR (CDCl₃) δ 6.02-5.80 (1H, m), 5.53-5.46 (2H, m), 5.37-5.21 (2H, m), 4.58 (2H, d, J = 5.5), 4.50-4.46 (0.5H, m), 4.34-4.25 (1H, m), 4.19-4.12 (0.5H, m), 3.06-2.77 (1H, m), 2.53-2.35 (1H, m), 1.85-1.50 (8H, m). Anal. Calcd for C₁₃H₁₉NO₅: C, 57.98; H, 7.11; N, 5.20. Found: C, 56.62; H, 7.22; N, 4.95. MS (ES⁺) 270.

(2*R*,3*S*) 3-Allyloxycarbonylamino-2-(indan-2-yloxy)-5-oxotetrahydrofuran (513c), was synthesized by a similar method as compound 513d/e to afford a single isomer (20%) as a pale yellow oil: $[\alpha]_D^{24} -63.1^\circ$ (c 0.2, CH₂Cl₂); IR (film) 3338, 2948, 1791, 1723, 1529, 1421, 1330, 1253, 1122, 984, 929, 746; ¹H NMR (CDCl₃) δ 7.20 (4H, m), 5.87 (1H, m), 5.61 (1H, d, J = 5.4), 5.33-5.10 (2H, m), 4.70 (1H, m), 4.56 (3H, m), 3.33-3.19 (2H, m), 3.10-2.94 (2H, m), 2.81 (1H, dd, J = 8.3, 17.3), 2.43 (1H, dd, J = 10.5, 17.3).

(2*R*,3*S*) 3-Allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydro-furan (513d) and (2*S*,3*S*) 3-Allyloxycarbonylamino-2-benzyloxy-5-oxo-tetrahydrofuran (513d/e), were prepared [via method described by Chapman Biorg. & Med. Chem. Lett., 2, pp. 615-618

- 631 -

(1992)]. Following work-up by extraction with ethylacetate and washing with NaHCO_3 , the product was dried (MgSO_4), filtered and evaporated to yield an oil which contained product and benzyl alcohol. Hexane (200ml) (200ml hexane for every 56g of AllocAsp(CO_2tBu) CH_2OH used) was added and the mixture stirred and cooled overnight. This afforded an oily solid. The liquors were decanted and retained for chromatography. The oily residue was dissolved in ethyl acetate and evaporated to afford an oil which was crystallised from 10% ethyl acetate in hexane (~500ml). The solid was filtered to afford **513d** (12.2g, 19%): mp. 108-110°C; $[\alpha]_D^{24} +75.72^\circ$ (c 0.25, CH_2Cl_2); IR (KBr) 3361, 1778, 1720, 1517, 1262, 1236, 1222, 1135, 1121, 944, 930, 760; ^1H NMR (CDCl_3) δ 7.38 (5H, m), 5.90 (1H, m), 5.50 (1H, s), 5.37 (0.5H, m), 5.26 (2.5H, m), 4.87 (1H, ABq), 4.63 (3H, m), 4.31 (1H, m), 3.07 (1H, dd), 2.46 (1H, dd). Anal. Calcd for $\text{C}_{15}\text{H}_{17}\text{NO}_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.85; H, 5.89; N, 4.80.

The liquors were combined and evaporated to yield an oil (~200g) containing benzyl alcohol. Hexane/ethyl acetate (9:1, 100ml) was added and the product purified by chromatography eluting with 10% ethyl acetate in hexane to remove the excess benzyl alcohol, and then dichloromethane/hexane (1:1 containing 10% ethyl acetate). This afforded **513e** containing some **513d** (20.5g, 32%): mp. 45-48°C; $[\alpha]_D^{24} -71.26^\circ$ (c 0.25, CH_2Cl_2); IR (KBr) 3332, 1804, 1691, 1536, 1279, 1252, 1125, 976. ^1H NMR (CDCl_3) δ 7.38 (5H, m), 5.91 (1H, m), 5.54 (1H, d, $J = 5.2$), 5.38 (3H, m); 4.90 (1H, ABq); 4.60 (4H, m), 2.86 (1H, dd); 2.52 (1H,

- 632 -

dd). Anal. Calcd for $C_{15}H_{17}NO_5 \cdot 0.1H_2O$ C, 61.47; H, 5.91; N, 4.78. Found: C, 61.42; H, 5.88; N, 4.81.

(2*RS*,3*R*) 3-(Allyloxycarbonylamino)-2-ethoxy-5-oxotetrahydrofuran (513f), was synthesized by a similar
 5 method as **513d/e** to afford a colourless oil (152mg, 79%): IR (film) 3334, 2983, 2941, 1783, 1727, 1713, 1547, 1529, 1422, 1378, 1331, 1313, 1164, 1122, 1060, 938; 1H NMR ($CDCl_3$) δ 6.09-5.82 (2H, m), 5.50-5.18 (3H, m), 4.64-4.54 (2H, m), 4.27-4.16 (1H, m), 3.95-3.78
 10 (1H, m), 3.73-3.56 (1H, m), 3.05-2.77 (1H, m), 2.56-2.37 (1H, m), 1.35-1.17 (4H, m). Anal. Calcd for $C_{10}H_{15}NO_5$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.16; H, 6.62; N, 5.99. MS (ES^+) 229 ($M^+ + 1$, 100%).

(3*S*,4*RS*) t-Butyl 3-(allyloxycarbonylamino)-4-hydroxy-5-(2-phenoxybenzoyloxy)pentanoate (513g). 4-Dimethylamino-pyridine (76.0mg, 622mmol) was added to a solution of 2-phenoxybenzoyl chloride (579mg, 2.49mmol) and **517** (600mg, 2.07mmol) in pyridine (10ml). The mixture was stirred at room temperature for 18h before
 20 adding brine (25ml) and extracting with ethyl acetate (30ml, 20ml). The combined organic extracts were washed with 1M hydrochloric acid (3 x 25ml), saturated aqueous sodium hydrogen carbonate (2 x 25ml) and brine (25ml), dried ($MgSO_4$) and concentrated. The pale
 25 orange oil was purified by flash column chromatography (1-10% acetone in dichloromethane) to afford 447mg (44%) of colourless oil: IR (film) 3375, 2980, 1721, 1712, 1602, 1579, 1514, 1484, 1451, 1368, 1294, 1250, 1234, 1161, 1137, 1081, 754; 1H NMR ($CDCl_3$) δ 7.98-7.93
 30 (1H, m), 7.50-7.41 (1H, m), 7.35-7.25 (2H, m), 7.22-7.03 (3H, m), 6.95 (3H, d), 5.95-5.76 (1H, m), 5.57

- 633 -

(1H, d), 5.30-5.13 (2H, m), 4.51 (2H, d), 4.25 (2H, d), 4.18-4.04 (1H, m), 3.88 (1H, m), 3.50 (1H, m), 2.51 (2H, m), 1.41 (9H, s). MS (ES⁺) 508 (57%), 503 (76), 486 (M⁺ + 1, 45), 468 (27), 412 (100). Accurate mass
 5 calculated for C₂₆H₃₂NO₈ (MH⁺): 486.2128. Found: 486.2158.

(3S,4R) t-Butyl (N-allyloxycarbonyl)-3-amino-4-hydroxy-5-(1-naphthoyloxy)pentanoate (513h), was prepared from
 (3S,4R) t-butyl (N-allyloxycarbonyl)-3-amino-4,5-
 10 dihydroxypentanoate by the method described for **513g** to afford 562mg (85%) of a colourless oil: IR(film) 3418, 2980, 1722, 1711, 1512, 1368, 1278, 1245, 1198, 1157, 1139; ¹H NMR (CDCl₃) δ 8.90 (1H, d, J = 8.6), 8.21 (1H, dd, J = 1.2, 7.3), 8.04 (1H, d, J = 8.2), 7.89 (1H, dd, J = 1.5, 7.9), 7.67-7.46 (3H, m), 5.88 (1H, m), 5.49
 15 (1H, d, J = 9.0), 5.35-5.18 (2H, m), 4.57-4.46 (4H, m), 4.19 (2H, m), 2.67 (2H, m), 1.40 (9H, s). Anal. Calcd for C₂₄H₂₉NO₇: C, 65.00; H, 6.59; N, 3.16. Found: C, 64.74; H, 6.56; N, 3.09. M.S. (ES⁺) 466 (M+Na, 100%), 444 (M+1, 39), 388 (44).

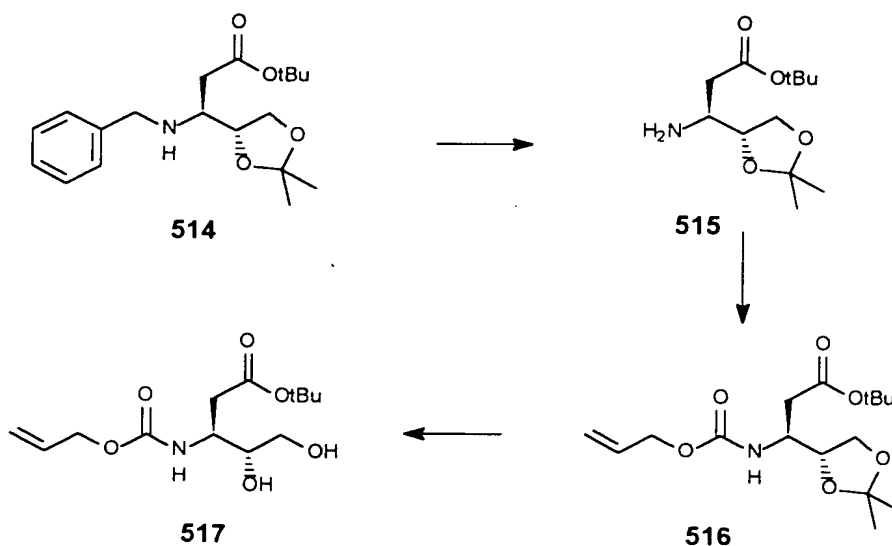
(3S,4RS) t-Butyl 3-(allyloxycarbonylamino)-4-hydroxy-5-(3-henoxybenzoyloxy)pentanoate (513i), was synthesized by a similar method as compound **513g** to afford a colourless oil (569mg, 85%): IR (film) 3400, 1723,
 25 1712, 1584, 1528, 1489, 1443, 1367, 1276, 1232, 1190, 1161, 1098, 1074, 995, 755; ¹H NMR (CDCl₃) δ 8.65-8.59 (1H, d), 7.84-7.66 (2H, m), 7.45-7.11 (5H, m), 7.05-6.97 (2H, m), 6.00-5.78 (1H, m), 5.54-5.14 (2H, m), 4.62-4.52 (2H, m), 4.42-4.32 (2H, m), 4.08-4.22 (2H, m),
 30 2.78-2.47 (2H, m), 1.44 (9H, s). MS (ES⁺) 508 (100%),

- 634 -

486 ($M^+ + 1$, 33. Accurate mass calculated for $C_{26}H_{32}NO_8$ (MH^+): 486.2128. Found: 486.2121.

(3*S*,4*RS*) *t*-Butyl 3-(allyloxycarbonylamino)-4-hydroxy-5-(5-methyl-3-phenylisoxazoloyloxy)pentanoate (513j), was synthesized by a similar method as compound 513g to afford a pale orange oil (905mg, 91%): IR (film) 3418, 3383, 2980, 1722, 1711, 1601, 1517, 1450, 1424, 1368, 1308, 1252, 1154, 1100, 994, 767, 698; 1H NMR ($CDCl_3$) δ 7.62-7.55 (2H, m), 7.51-7.42 (3H, m), 5.98-5.76 (1H, m), 5.33-5.18 (2H, m), 4.53 (2H, d), 4.18 (2H, d), 3.91 (1H, m), 3.80 (1H, m), 2.76 (3H, s), 2.50 (2H, m), 1.43 (9H, s). Anal. Calcd for $C_{24}H_{30}N_2O_8 \cdot 0.5H_2O$: C, 59.62; H, 6.46; N, 5.79. Found: C, 59.46; H, 6.24; N, 5.72. MS (ES^+) 497 (100%), 475 ($M^+ + 1$, 15), 419 (48).

15



(3*S*,4*R*) *t*-Butyl 3-benzylamino-4,5-(dimethylmethylenedioxy)-pentanoate (514), was prepared by the method described in H. Matsunaga, et al.

- 635 -

Tetrahedron Letters 24, pp. 3009-3012 (1983) as a pure diastereomer (60%) as an oil: $[\alpha]_D^{23}$ -36.9° (c 0.5, dichloromethane); IR (film) 2982, 2934, 1726, 1455, 1369, 1257, 1214, 1157, 1068; ^1H NMR (CDCl_3) δ 7.31 (5H, m), 4.10 (1H, q, J = 6.0), 4.05-3.75 (4H, m), 3.10 (1H, q, J = 6.0), 2.40 (2H, m), 1.42 (9H, s), 1.40 (3H, s), 1.34 (3H, s).

(3S,4R) t-Butyl 3-(allyloxycarbonylamino)-4,5-(dimethylmethylenedioxy)pentanoate (516). **514** (3.02g, 9.00mmol) and 10% palladium on carbon (300mg) in ethanol (30ml) were stirred under hydrogen for 2h. The suspension was filtered through celite and a 0.45mm membrane and the filtrate concentrated to give a colourless oil **515** (2.106g, 95%) which was used without purification. The oil (1.93g, 7.88mmol) was dissolved in water (10ml) and 1,4-dioxan and sodium hydrogen carbonate added (695mg, 8.27mmol). The mixture was cooled to 0°C and allyl chloroformate (1.04g, 9.19ml, 8.66mmol) added dropwise. After 3h the mixture was extracted with ether (2 x 50ml). The combined ether extracts were washed with water (2 x 25ml) and brine (25ml), dried (MgSO_4) and concentrated to give a colourless oil. Flash column chromatography (10-35% ethylacetate in hexane) afforded a colourless solid (2.69g, 95%): mp. 64-5°C; $[\alpha]_D^{23}$ -21° (c 1.00, CH_2Cl_2); IR (KBr) 3329, 1735, 1702; ^1H NMR (CDCl_3) δ 6.00-5.82 (1H, m), 5.36-5.14 (2H, m), 5.42 (1H, s), 4.56 (1H, d), 4.40-4.08 (2H, m), 4.03 (1H, m), 3.70 (1H, m), 2.52 (2H, m), 1.44 (12H, 2 x s), 1.33 (3H, s); Anal. Calcd for $\text{C}_{16}\text{H}_{27}\text{NO}_6$: C, 58.34; H, 8.26; N, 4.25. Found: C, 58.12; H, 8.16; N, 4.19; MS (+FAB) 320 ($\text{M}^+ + 1$, 41%), 274 (70), 216 (100).

- 636 -

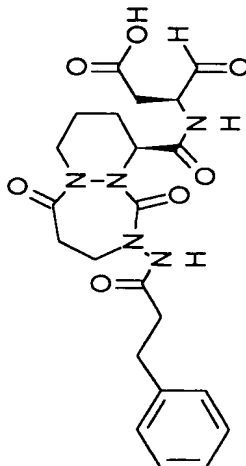
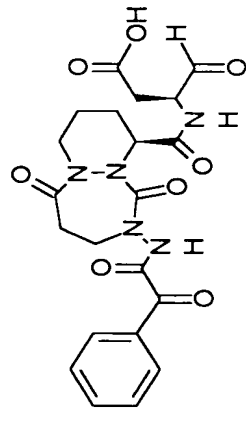
(3*S*,4*R*) *t*-Butyl 3-(allyloxycarbonylamino)4,5-dihydroxy pentanoate (517). A solution 516 (2.44g, 7.41mmol) in 80% aqueous acetic acid (25ml) was stirred at room temperature for 24h then concentrated and azeotroped with toluene (2 x 25ml). The residue was treated with brine (25ml) and extracted with ethylacetate (2 x 25ml). The organic fractions were dried (MgSO₄) and concentrated to afford a colourless oil. Flash chromatography (20-80% ethyl acetate in dichloromethane) gave a colourless solid (1.99g, 90%): mp. 74-5°C; $[\alpha]_D^{25}$ -1.3° (c 1.0, CH₂Cl₂); IR (KBr) 1723, 1691; ¹H NMR (CDCl₃) δ 6.02-5.78 (2H, m), 5.35-5.16 (2H, m), 4.55 (2H, d), 4.16-4.04 (2H, m), 2.76 (2H, s), 3.56 (2H, m), 2.56 (2H, m), 1.43 (9H, s); Anal. Calcd for C₁₃H₂₃NO₆ : C, 53.97; H, 8.01; N, 4.84. Found : C, 53.79; H, 7.88; N, 4.81; MS(+FAB) 290 (M⁺+1, 44%), 234 (100).

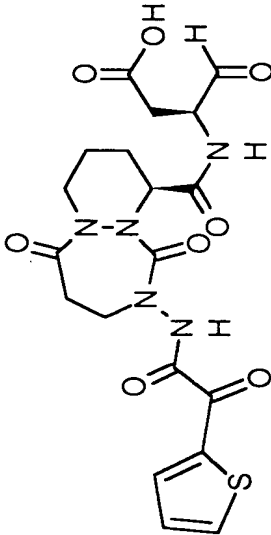
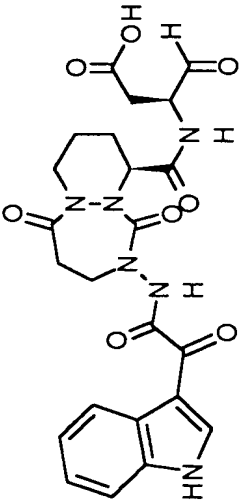
Example 30

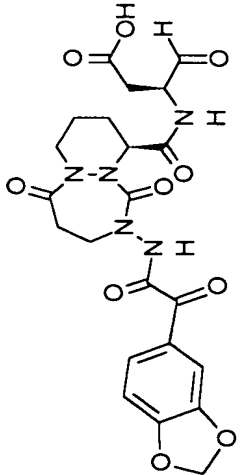
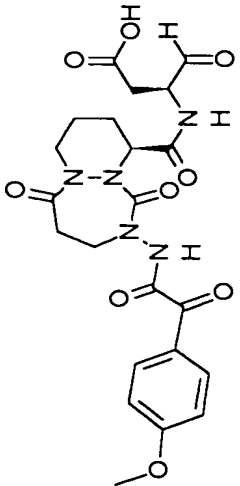
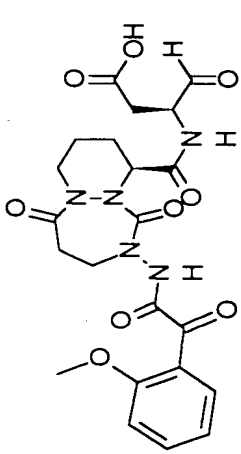
Compounds 1105-1125 were prepared as follows.

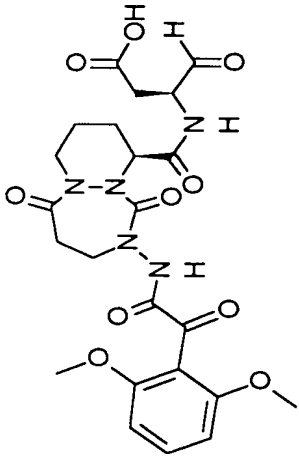
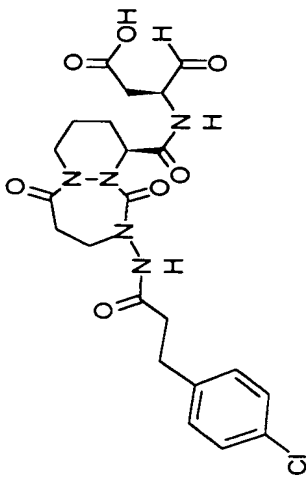
Physical data for these compounds is listed in Table 24.

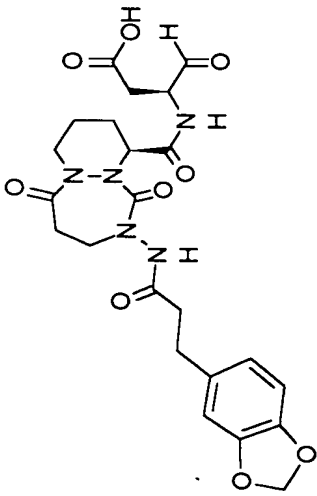
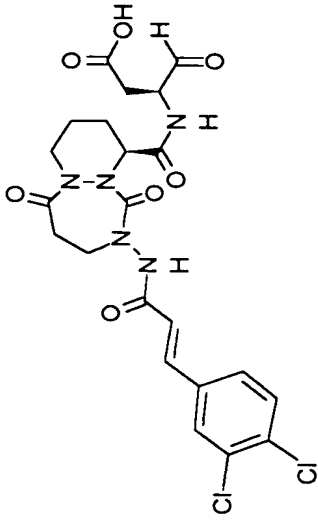
Table 24

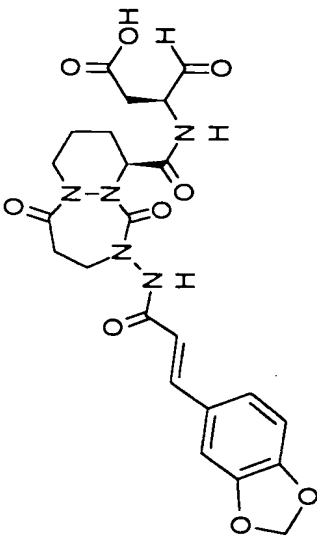
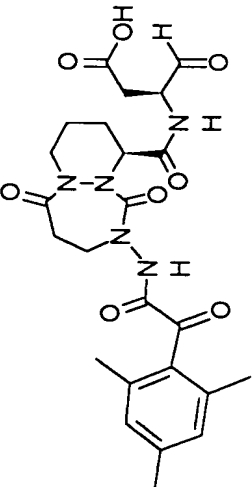
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na) +
1105		C22H27N5O7	473.49	12.769 (1) 99%	496.9
1106		C21H23N5O8	473.45	12.137 (1) 99%	496.9

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na) +
1107		C19H21N5O8S	479.47	11.272 (1) 97%	502.9
1108		C23H24N6O8	512.48	13.699 (1) 97%	536.4

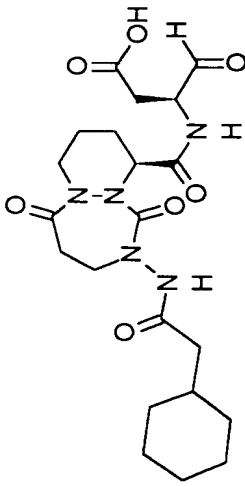
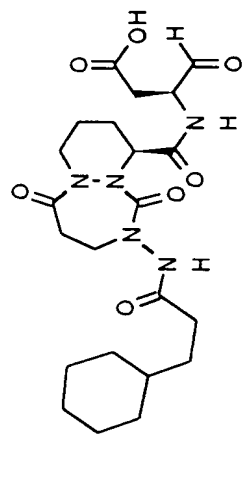
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1109		C22H23N5O10	517.46	12.341 (1) 92%	541.2
1110		C22H25N5O9	503.47	12.991 (1) 96%	527.9
1111		C22H25N5O9	503.47	10.951 (1) 99%	526.7

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na) +
1112		C23H27N5O10	533.50	11.377 (1) 98%	557.2
1113		C22H26ClN5O7	507.93	16.317 (1) 98%	531.5

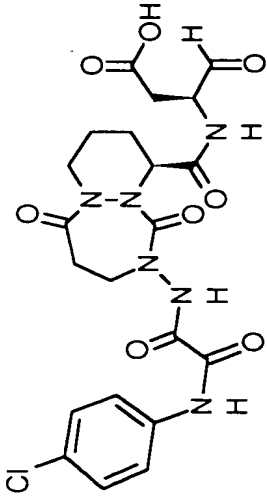
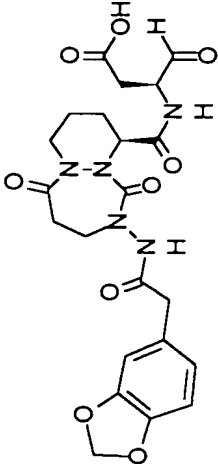
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1114		C23H27N5O9	517.50	12.902 (1) 99%	542.4
1115		C22H23Cl2N5O7	540.36	12.529 (2) 97%	563.4

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1116		C23H25N5O9	515.48	14.144 (1) 85%	538.8
1117		C24H29N5O8	515.53	11.551 (2) 97%	538.8

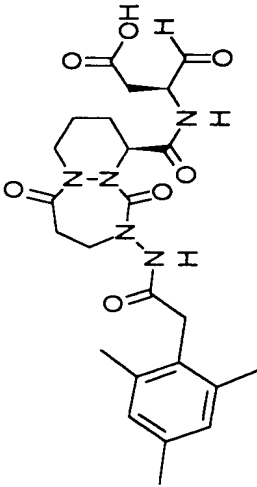
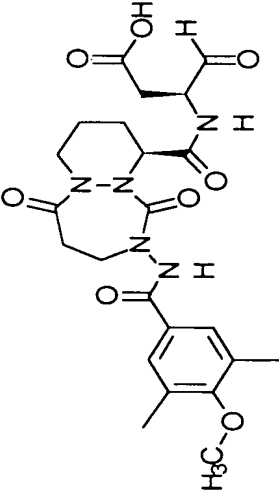
- 643 -

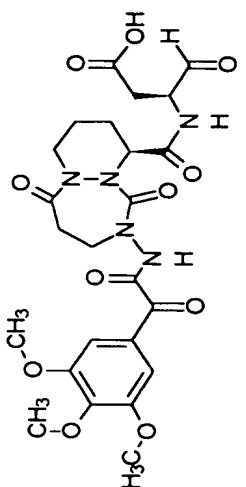
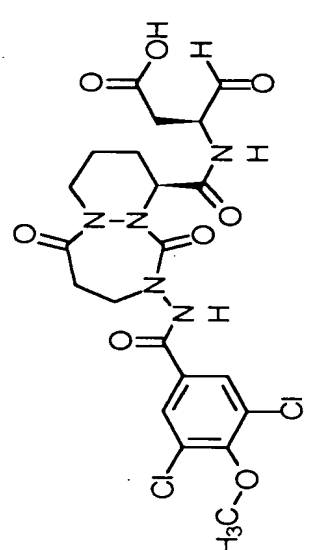
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1118		C21H31N5O7	465.51	13.974 (1) 96%	488.9
1119		C22H33N5O7	479.54	11.079 (2) 95%	502.9

- 644 -

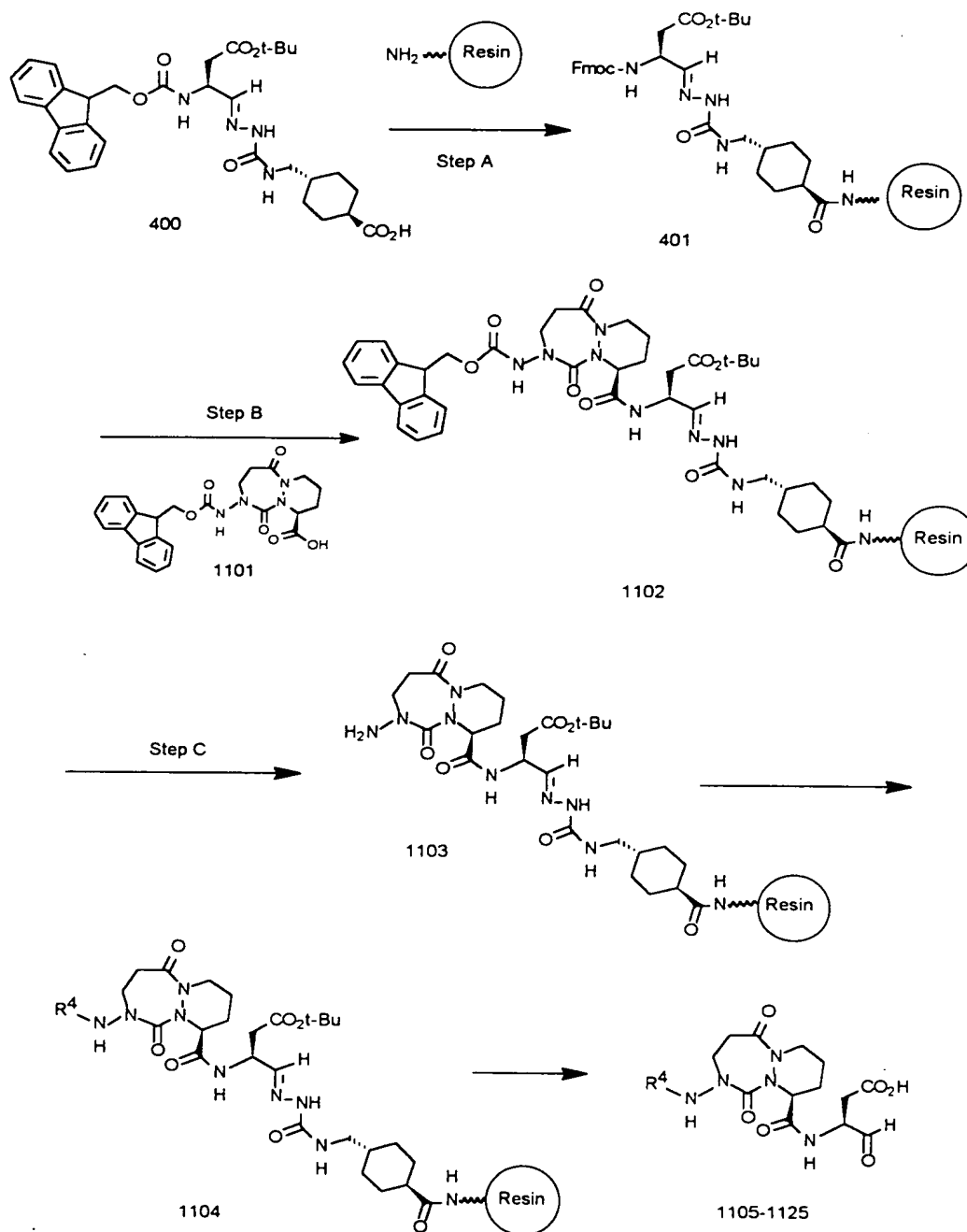
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1120		C21H23ClN6O8	522.91	16.796 (1) 99%	547.3
1121		C22H25N5O9	503.47	11.131 (1) 99%	527.9

- 645 -

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1122		C ₂₄ H ₃₁ N ₅ O ₇	501.54	10.892 (2) 98%	525.5
1123		C ₂₆ H ₂₄ N ₄ O ₁₀	552.50	15.85 >0.98	574

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na) +
1124		C24H29N5O11	563.53	13.336 (1) 99%	587
1125		C21H23Cl2N5O8	544.35	8.99 0.95	566

- 647 -



Step A. Synthesis of 401. TentaGel S® NH_2 resin (0.25 mmol/g, 5.25 g) was placed in a sintered glass shaker vessel and washed with dimethylacetamide (3 X 15 mL). Compound **400** (1.36 g, 2.3 mmol) was

- 648 -

dissolved in DMA (10 mL) and O-benzotriazole-N,N,N,N'-tetramethyluronium hexafluorophosphate (HBTU; 0.88 g, 2.3 mmol), and DIEA (0.8 mL, 4.6 mmol) were added. The solution was transferred to the resin and a further 5 mL DMA added. The reaction mixture was agitated for 1.5 h at room temperature using a wrist arm shaker. The resin was filtered and washed with dimethylacetamide (4 X 15 mL).

Step B. Synthesis of 1102. Resin 401 was deprotected with 20% (v/v) piperidine/dimethylacetamide (15 mL) for 10 min (shaking) and then for 10 min with fresh piperidine reagent (15 mL). The resin was then washed with dimethylacetamide (6 X 15 mL), followed by N-methylpyrrolidone (2 X 25 mL).

Compound 1101 (0.979 g, 2.11 mmol) was dissolved in dimethylacetamide (8 mL). HBTU (0.81 g, 2.1 mmol) and DIEA (0.75 mL, 4.3 mmol) were added and the solution added to the resin, followed by dimethylacetamide (4 mL). The reaction mixture was agitated for 2 h at room temperature using a wrist arm shaker. The resin work-up was performed as described for 401 to yield 1102.

Step C. Synthesis of 1103. This compound was prepared from resin 1102 (0.040 mmol) using an Advanced ChemTech 396 Multiple Peptide synthesizer. The automated cycles consisted of a resin wash with dimethylformamide (2 X 1 mL), deprotection with 25% (v/v) piperidine in dimethylformamide (1 mL) for 3 min followed by fresh reagent (1 mL) for 10 min to yield resin 1103. The resin was washed with

- 649 -

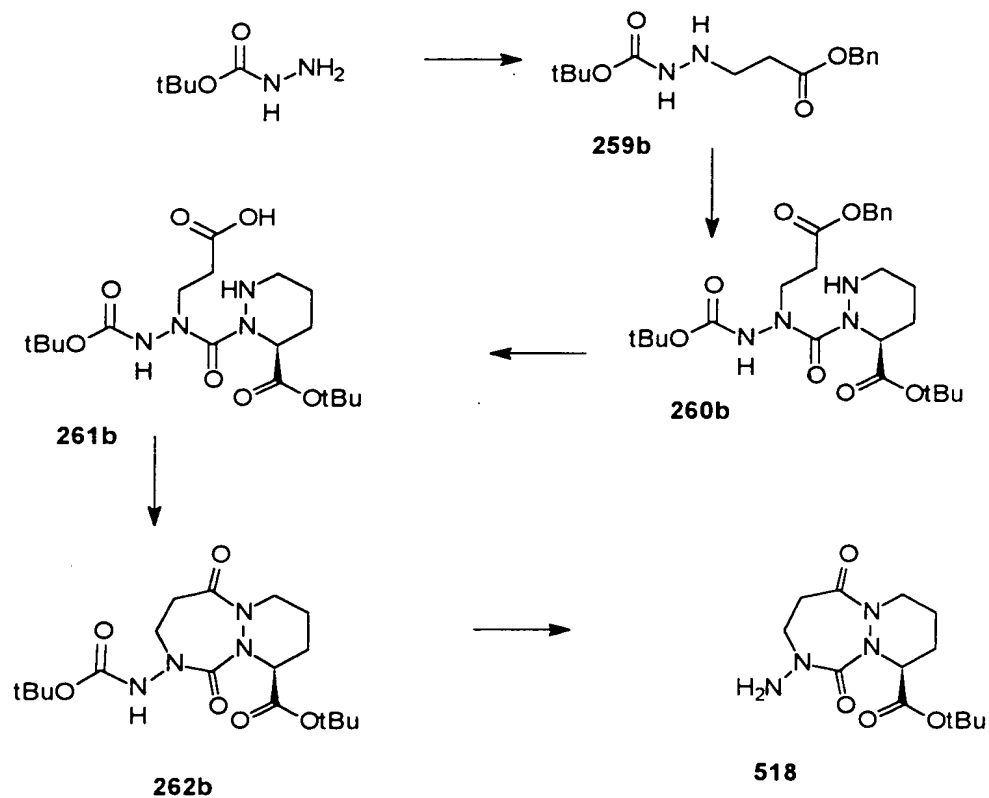
dimethylformamide (3 X 1 mL) and N-methylpyrrolidone (3 X 1 mL).

Resin **1103** was acylated with a solution of 0.4M carboxylic acid and 0.4M HOBT in N-methylpyrrolidone (0.5 mL), a solution of 0.4M HBTU in N-methylpyrrolidone (0.5 mL) and a solution of 1.6M DIEA in N-methylpyrrolidone (0.25 mL) and the reaction was shaken for 2 hr at room temperature. The acylation step was repeated. Finally, the resin was washed with N-methylpyrrolidone (1 X 1 mL), dimethylformamide (4 X 1 mL), dichloromethane (5 X 1 mL) and dried *in vacuo*. The aldehyde was cleaved from the resin and globally deprotected by treatment with 95% TFA/ 5% H₂O (v/v, 1.5 mL) for 30 min at room temperature. After washing the resin with cleavage reagent (1 mL), the combined filtrates were added to cold 1:1 ether:hexane (10 mL) and the resulting precipitate was isolated by centrifugation and decantation. The resulting pellet was dissolved in 10% acetonitrile/90% H₂O/0.1% TFA (5 mL) and lyophilized to obtain crude **1105-1125** as a white powder. The compound was purified by semi-preparative RP-HPLC with a Rainin Microsorb™ C18 column (5 μ, 21.4 X 250 mm) eluting with a linear acetonitrile gradient (8% - 48%) containing 0.1% TFA (v/v) over 30 min at 12 mL/min. Fractions containing the desired product were pooled and lyophilized to provide **1105-1125** (10.8 mg, 63%).

- 650 -

Analytical HPLC methods:

- (1) Waters DeltaPak C18, 300Å (5μ, 3.9 X 150 mm).
Linear acetonitrile gradient (0% - 25%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.
- 5 (2) Waters DeltaPak C18, 300Å (5μ, 3.9 X 150 mm).
Linear acetonitrile gradient (5% - 45%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.



Benzyl 3-(N'-t-butyloxycarbonylhydrazino)propionate (259b), was synthesized via method used to prepare 259 from 258 to afford a waxy solid (87g, 51%): mp 54-55°C; IR (film) 3324, 2978, 1732, 1713, 1455, 1367, 1277,

- 651 -

1254, 1171; ^1H NMR (CDCl_3) δ 7.35 (5H, m), 6.15 (1H, bs),
 5.13 (2H, s), 3.15 (2H, t, $J = 6.5$), 2.54 (2H, t, $J =$
 6.5), 1.45 (9H, s). Anal. Calcd for $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_3$: C,
 61.21; H, 7.53; N, 9.52. Found: C, 61.29; H, 7.51; N,
 5 9.51. MS (ES^+) 295 ($\text{M}^+ + 1$).

**(3S) 1-Benzyl 3-*t*-butyl 2-(*N*-2-benzyloxycarbonylethyl-
 NI-2-butoxycarbonylhydrazino)carbonyl
 hexahydropyridazine dicarboxylate (260b)**, was
 synthesized via method used to prepare 260 from 259 to
 10 afford a gum (81g) which was used in the next step
 without purification. Analytical data for a pure
 sample: IR (film) 3318, 2976, 1733, 1451, 1412, 1393,
 1366, 1256, 1161; ^1H NMR (CDCl_3) δ 7.34 (10H, m), 6.68
 (0.5H, bs), 5.11 (4H, m), 4.63 (0.5H, bs), 4.14 (1H,
 15 m), 3.53 (2H, m), 3.08 (1H, m), 2.63 (2H, m), 2.10-1.60
 (4H, m), 1.60-1.35 (19H, m + 2 x s).

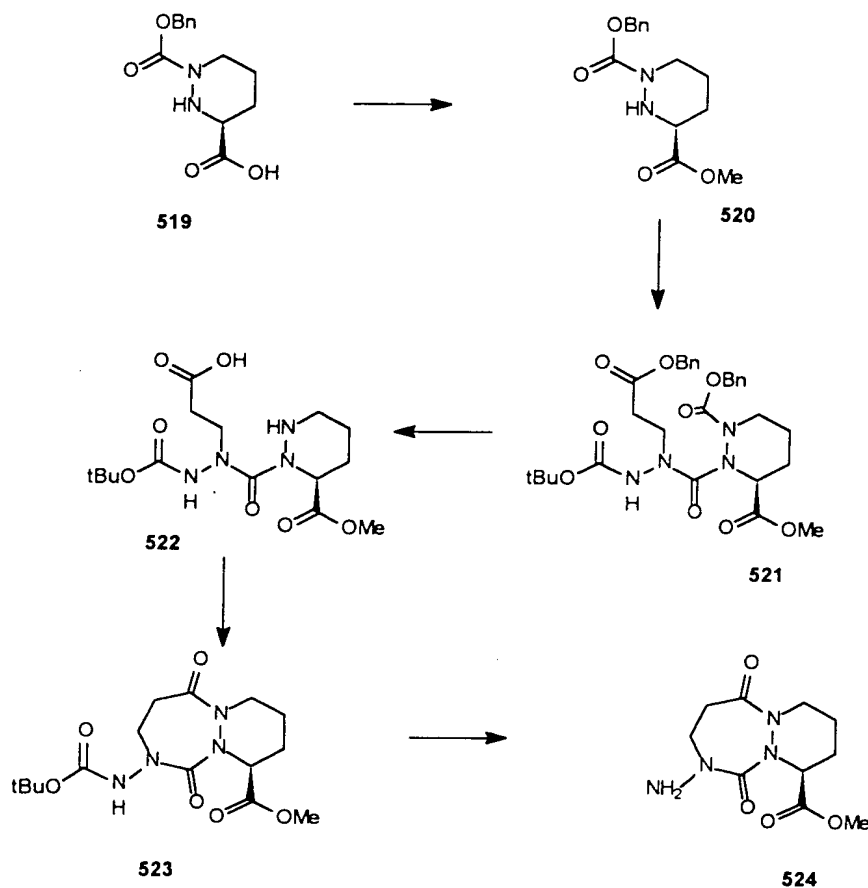
**(3S) *t*-Butyl 2-(*N'*-*t*-butoxycarbonyl-*N*-2-
 carboxyethylhydrazino)-carbonylhexahydropyridazine 3-
 carboxylate (261b)**, was synthesized via method used to
 20 prepare 261 from 260 to give a gum which was purified
 by flash chromatography (1:1 ethyl
 acetate/dichloromethane) to give the title compound
 261b (36.0g, 79.4% over 2 stages): IR (film) 3267,
 2979, 2937, 1728, 1668, 1394, 1369, 1245, 1159; ^1H NMR
 25 (CDCl_3) δ 7.6 (1H, bs), 6.8 (1H, vbs), 4.47 (1H, bs),
 3.73 (2H, bs), 2.98 (1H, bs), 2.66 (3H, m), 2.04 (1H,
 bs), 1.84 (1H, m), 1.6-1.2 (21H, m + s).

**(4S) *t*-Butyl 7-*t*-butoxycarbonylamino-6,10-dioxo-
 1,2,3,4,7,8,9,10-octahydro-6H-**

- 652 -

- pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262b), was synthesized via method used to prepare 262 from 261 to give the title compound 262b, (18.6g, 54%) as an oil: $[\alpha]_D^{20} +47.7^\circ$ (c 0.236, CH_2Cl_2); IR (film) 3291, 2978, 1738, 1727, 1690, 1678, 1439, 1243, 1164; ^1H NMR (CDCl_3) δ 6.59 (1H, s), 5.06 (1H, m), 4.47 (1H, m), 3.85 (3H, m), 2.82 (1H, m), 2.37 (1H, m), 2.22 (1H, m), 1.92 (1H, m), 1.63 (2H, m), 1.48 and 1.46 (18H, 2 x s). MS (ES^+) 399 ($\text{M}^+ + 1$).
- 10 (4S) t-Butyl 7-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (518). Compound 262b (2.43g, 6.1mmol) was dissolved in 1M hydrogen chloride in ethyl acetate (30ml) and stirred at room temperature for 20h. Solid sodium bicarbonate (4g, 46.5mmol) and water 20ml were added and the mixture stirred for 5min before separating and extracting the aqueous portion with ethyl acetate. The combined organic solution was washed with water, saturated salt, dried (MgSO_4) and concentrated. Purification by flash chromatography (50% ethyl acetate in dichloromethane - 100% ethyl acetate) gave the pure product 518 (1.08g, 59%) as an unstable oil: $[\alpha]_D^{20} +82^\circ$ (c 0.55, CH_2Cl_2); IR (film) 3331, 2977, 1731, 1680, 1664, 1439, 1420, 1315, 1158; ^1H NMR (CDCl_3) δ 5.08 (1H, m), 4.48 (1H, m), 3.80 (2H, Abq), 3.70 (2H, bs, exch with D_2O), 3.53 (1H, m), 2.75 (1H, m), 2.30 (2H, m), 1.88 (1H, m), 1.71 (2H, m), 1.47 (9H, s).

- 653 -



(3*S*) Methyl 1-benzyloxycarbonyl-hexahydropyridazine-3-carboxylate (520). 519 (9.4g, 35.6mmol) was suspended in methanol (230ml) and cooled to 0°C in an ice bath. Thionyl chloride (3ml, 4.89g, 41.1mmol) was added dropwise over 30min and the mixture stirred at ambient temperature for 48h. The solvent was removed in vacuo at 30°C and the oily residue dissolved in ethyl acetate (500ml). The organic solution was washed with saturated sodium bicarbonate, water and brine, dried (MgSO₄) and concentrated to give 520 (7.84g, 79%) as an oil: $[\alpha]_D^{22}$ -25.9° (c 0.615, CH₂Cl₂); IR (film) 2953, 1739, 1703, 1694, 1440, 1403, 1357, 1261, 1241, 1174; ¹H NMR (CDCl₃) δ 7.36 (5H, s), 5.18 (2H, s), 4.00 (1H,

- 654 -

bd), 3.73 (3H, s), 3.55 (1H, dd), 3.12 (1H, t), 2.06 (1H, m), 1.73 (3H, m). Anal. Calcd for $C_{14}H_{17}N_2O_4 \cdot 0.25H_2O$: C, 59.46; H, 6.59; N, 9.91. Found: C, 59.44; H, 6.46; N, 10.09.

- 5 **(3S) 1-Benzyl 3-methyl 2-(N-2-benzyloxycarbonylethyl-NI-t-butoxycarbonylhydrazino)carbonyl hexahydropyridazine dicarboxylate (521).** Using a similar method to that described for 260 above, 521 was prepared, 96% as a crude oil: $[\alpha]_D^{22} -22.16^\circ$ (c 0.25, CH₂Cl₂); IR (film) 3316, 2976, 2953, 1738, 1726, 1714, 1690, 1367, 1260, 1167; ¹H NMR (CDCl₃) δ 7.25 (10H, m), 6.82 (1H, bs), 5.10 (4H, m), 4.80 (1H, bs), 4.3-3.4 (6H, m), 3.10 (1H, m), 2.59 (2H, m), 1.95 (2H, m), 1.44 (10H, m + s).
- 10
- 15 **(3S) Methyl 2-(N'-t-butoxycarbonyl-N-2-carboxyethylhydrazino)-carbonyl hexahydropyridazine 3-carboxylate (522).** Using a similar method to that described for 261 above, 522 was prepared, 92% as a white solid: mp. 146-148°C (decomp); $[\alpha]_D^{22} +27.8^\circ$ (c 0.25, CH₂Cl₂); IR (KBr) 3346, 1740, 1710, 1626, 1497, 1290, 1250, 1206, 1179, 1159; ¹H NMR (CDCl₃) δ 7.60 (1H, bs), 7.5-5.5 (1H, vbs), 4.64 (1H, bs), 3.76 (5H, m + s), 3.00 (1H, m), 2.70 (3H, m), 2.16 (1H, m), 1.92 (1H, m), 1.56 (1H, m), 1.46 (11H, m + s). Anal. Calcd for $C_{15}H_{26}N_4O_7$: C, 48.12; H, 7.00; N, 14.96. Found: C, 48.21; H, 6.96; N, 14.86. MS (ES⁺) 373 (M⁻ - 1).
- 20
- 25

(4S) Methyl 7-t-butoxycarbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (523).

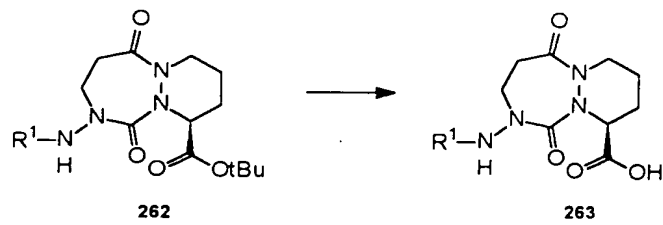
- 655 -

522 (7.15g, 19.1mmol) was dissolved in dichloromethane(100ml), containing dimethylformamide (0.5ml), and cooled to 0°C. Thionyl chloride (1.6ml, 2.61g, 22mmol) and N-ethyl morpholine (4.86ml, 440mg, 38.2mmol) were added and the mixture stirred for 2h. The organic mixture was washed with 2M sodium bisulphate (50ml), saturated sodium bicarbonate (50ml) and brine (50ml), dried (MgSO₄) and concentrated. The residues were triturated with ether to give 523 as a white solid (5.73g, 84%): mp. 186-188°C (decomp); $[\alpha]_D^{22} +65.3^\circ$ (c 0.25, CH₂Cl₂); IR (KBr) 3298, 2978, 1750, 1720, 1682, 1658, 1455, 1423, 1369, 1316, 1241, 1212, 1160; ¹H NMR (CDCl₃) δ 6.56 (1H, s), 5.17 (1H, dd), 4.48 (1H, bd), 3.81 (3H, m), 3.75 (3H, s), 2.83 (1H, dt), 2.40 (1H, m), 2.28 (1H, m), 1.95 (1H, m), 1.67 (1H, m), 1.47 (9H, s). Anal. Calcd for C₁₅H₂₄N₄O₆•1/6H₂O: C, 50.13; H, 6.82; N, 15.59. Found: C, 50.12; H, 6.71; N, 15.58. MS (ES⁺) 357 (M⁺ - 1, 46%), 301 (100%).

(4S) Methyl 7-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (524), was synthesized from 523 via method used to prepare 518.

Compounds 262a-k were synthesized via methods used to prepare 211b-f.

- 656 -



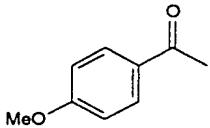
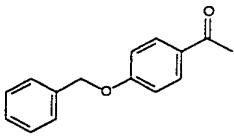
262a-k

263a-k

compound	R
262a 263a	
262b 263b	
262c 263c	
262d 263d	
262e 263e	
262f 263f	
262g 263g	
262h 263h	

- 657 -

20

262i 263i	
262j 263j	PhSO ₂ —
262k 263k	

25 (4S) t-Butyl 6,10-dioxo-7-(2-naphthyl) sulfonamide-
 1,2,3,4,7,8,9,10-octahydro-6H-
 pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate
 (262a). 443mg (91%) of the title compound was
 obtained: mp. 56-7°C; $[\alpha]_D^{25} +76^\circ$ (c 0.15, CH₂Cl₂); IR
 30 (KBr) 3429, 2979, 1734, 1675, 1418, 1369, 1339, 1323,
 1244, 1164, 665; ¹H NMR (CDCl₃) δ 8.45 (1H, s), 8.00-7.59
 (7H, m), 4.69-4.65 (1H, m), 4.25-4.12 (1H, m), 4.10-
 3.99 (1H, m), 3.73-3.55 (2H, m), 2.40-2.30 (1H, m),
 1.99-1.91 (1H, m), 1.82-1.62 (2H, m), 1.48-1.46 (2H,
 35 m), 1.37 (9H, s). Anal. Calcd for C₂₃H₂₈N₄O₆S•H₂O: C,
 54.53; H, 5.97; N, 11.06. Found: C, 54.60; H, 5.73; N,
 10.95. MS (ES⁺) 489.

(4S) t-Butyl 6,10-dioxo-7-(3-methoxyphenylureido)-
 1,2,3,4,7,8,9,10-octahydro-6H-
 40 pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate
 (262c), 120mg (80%) of colourless foam was obtained:

- 658 -

$[\alpha]_D^{22} +22.6^\circ$ (c 0.1, CH_2Cl_2); IR (KBr) 3316, 1732, 1671, 1609, 1551, 1495, 1455, 1432, 1316, 1288, 1245, 1218, 1158, 1122, 1023; ^1H NMR (CDCl_3) δ 7.16 (4H, m), 6.79 (1H, m) 6.60 (1H, m), 5.11 (1H, m), 4.59 (1H, m),
 5 3.89 (2H, m), 3.77 (3H, s), 3.72 (2H, m), 2.85 (1H, m).

(4S) t-Butyl 6,10-dioxo-7-(2-methoxyphenylureido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino [1,2-a][1,2,4]triazepine-4-carboxylate (262d), (81%) was obtained as colourless foam: $[\alpha]_D^{22} +3.7^\circ$ (c 0.1,
 10 CH_2Cl_2); IR (KBr) 3468, 3446, 3269, 1734, 1698, 1667, 1609, 1555, 1490, 1461, 1433, 1423, 1296, 1246, 1215, 1173, 1157, 1028, 756; ^1H NMR (CDCl_3) δ 8.23 (1H, m), 7.95 (1H, s), 6.95 (4H, m), 5.15 (1H, m), 4.60 (1H, m), 3.98-3.65 (4H, m), 3.89 (3H, s), 2.90 (1H, m), 2.48
 15 (1H, m), 2.25 (1H, m), 2.05-1.65 (2H, m), 1.48 (9H, s).

(4S) t-Butyl 6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylacetylamino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262e), was obtained as a white foamy solid (155mg, 53%): mp. 53-7°C; $[\alpha]_D^{22} +57.4^\circ$ (c 0.1, CH_2Cl_2); IR (KBr) 3271, 2978, 1733, 1680, 1437, 1314, 1245, 1156; ^1H NMR (CDCl_3) δ 7.46 (1H, s), 7.42-7.20 (5H, m), 5.03 (1H, dd), 4.52-4.40 (1H, m), 3.96-3.70 (2H, m), 3.70-3.49 (1H, m), 3.63 (2H, s), 2.92-2.75 (1H, m), 2.43-
 25 2.33 (1H, m), 2.33-2.15 (1H, m), 2.00-1.50 (3H, m), 1.45 (9H, s). Anal. Calcd for $\text{C}_{21}\text{H}_{28}\text{N}_4\text{O}_5 \cdot 0.25\text{H}_2\text{O}$: C, 59.91; H, 6.82; N, 13.31. Found: C, 60.19; H, 6.80; N, 13.30. MS (ES^+) 418 ($\text{M}^+ + 2$, 25%), 417 ($\text{M}^+ + 1$, 100), 362 (9), 361 (45).

- 659 -

(4S) t-Butyl 6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-(3-phenylureido)-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262f), was obtained as a white solid (273mg, 93%): mp. 102-6°C; $[\alpha]_D^{22} +7.5^\circ$ (c 0.07, CH₂Cl₂); IR (KBr) 3320, 2979, 1731, 1676, 1669, 1601, 1549, 1444, 1314, 1240, 1156; ¹H NMR (CDCl₃) δ 7.37-7.20 (6H, m), 7.08-6.98 (1H, m), 5.12 (1H, dd), 4.64-4.55 (1H, m), 4.02-3.78 (2H, m), 3.75-3.65 (1H, m), 2.94-2.75 (1H, m), 2.57-2.35 (1H, m), 2.35-2.20 (1H, m), 2.00-1.50 (3H, m), 1.48 (9H, s). Anal. Calcd for C₂₀H₂₇N₅O₅•0.4H₂O: C, 56.56; H, 6.60; N, 16.49. Found: C, 56.89; H, 6.58; N, 16.07. MS (ES⁺) 419 (M⁺ + 2, 24%), 418 (M⁺ + 1, 100), 363 (15), 362 (81), 242 (10).

(4S) t-Butyl 6,10-dioxo-7-(indole-2-carboxamido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262g), (13g) was obtained as a white solid (298mg, 70%): mp. 138-43°C; $[\alpha]_D^{23} +69.8^\circ$ (c 0.1, CH₂Cl₂); IR (KBr) 3282, 2978, 1733, 1664, 1536, 1421, 1310, 1156, 748; ¹H NMR (CDCl₃) δ 9.67 (1H, s), 9.53 (1H, s), 7.50 (1H, d), 7.30-7.15 (2H, m), 7.10-7.00 (1H, m), 6.93 (1H, s), 5.16-5.12 (1H, m), 4.60-4.50 (1H, m), 4.05-3.85 (2H, m), 3.85-3.70 (1H, m), 3.05-2.90 (1H, m), 2.55-2.35 (1H, m), 2.35-2.20 (1H, m), 2.00-1.85 (1H, m), 1.85-1.50 (2H, m), 1.47 (9H, s). Anal. Calcd for C₂₂H₂₇N₅O₅•0.45H₂O: C, 58.77; H, 6.26; N, 15.58. Found: C, 59.14; H, 6.24; N, 15.18. MS (ES⁺) 433 (M⁺ + 2, 26%), 442 (M⁺ + 1, 100), 387 (17), 386 (79), 285 (20), 229 (85), 211 (26), 185 (15), 183 (57), 139 (9).

- 660 -

(4S) t-Butyl 7-[(4-acetamido)benzamido]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]-triazepine-4-carboxylate (262h), was obtained as a white solid (325mg, 73%): mp. 209-12°C; $[\alpha]_D^{24} +62.4^\circ$ (c 0.2, CH₂Cl₂); IR (KBr) 3513, 3269, 2980, 1731, 1680, 1653, 1599, 1531, 1314, 1158; ¹H NMR (CDCl₃) δ 9.40 (1H, s), 8.75 (1H, s), 7.72 (2H, d), 7.47 (2H, d), 5.15-5.05 (1H, m), 4.55-4.45 (1H, m), 4.05-3.70 (3H, m), 3.00-2.80 (1H, m), 2.45-2.35 (1H, m), 2.30-2.15 (1H, m), 2.10 (3H, s), 2.00-1.80 (1H, m), 1.80-1.50 (2H, m), 1.48 (9H, s). Anal. Calcd for C₂₂H₂₉N₅O₆: C, 57.51; H, 6.36; N, 15.24. Found: C, 57.41; H, 6.38; N, 15.12. MS (ES⁺) 461 (M⁺ + 2, 26%), 460 (M⁺ + 1, 100), 405 (12), 404 (55), 354 (7), 285 (23), 229 (52), 183 (22).

(4S) t-Butyl 6,10-dioxo-7-(4-methoxybenzoylamino)-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-carboxylate (262i), was obtained as a white glassy solid (76%): mp. 85-9°C; $[\alpha]_D^{25} +66.4^\circ$ (c 0.11, CH₂Cl₂); IR (KBr) 1732, 1668, 1607, 1502, 1440, 1312, 1295, 1258, 1176, 1157, 1025; ¹H NMR (CDCl₃) δ 8.25 (1H, s), 7.77 (2H, m), 6.90 (2H, m), 5.11-5.07 (1H, m), 4.55-4.48 (1H, m), 4.01-3.91 (2H, m), 3.86-3.78 (1H, m), 3.85 (3H, s), 2.98 (1H, m), 2.46-2.40 (1H, m), 2.26-2.20 (1H, m), 2.05-1.80 (1H, m), 1.70-1.64 (2H, m), 1.48 (9H, s).

(4S) t-Butyl 6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylsulphonylamino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262j), was obtained as a white crystalline solid (79%): mp. 182-3°C (dec); $[\alpha]_D^{22} +92.1^\circ$ (c 0.4, CH₂Cl₂);

- 661 -

IR (KBr) 3283, 1732, 1684, 1448, 1430, 1404, 1369, 1338, 1306, 1285, 1242, 1169, 1091, 692; ^1H NMR (CDCl_3) δ 7.89 (2H, d, $J = 7.4$), 7.76 (1H, s), 7.64-7.49 (3H, m), 4.83 (1H, m), 4.35 (1H, brd, $J = 13.0$), 4.00 (1H, m), 3.74-3.63 (2H, m), 2.39-2.26 (2H, m), 2.06 (1H, m), 1.50-1.41 (10H, m). Anal. Calcd for $\text{C}_{19}\text{H}_{26}\text{N}_4\text{O}_6$: C, 52.04; H, 5.98; N, 12.78. Found: C, 52.11; H, 5.95; N, 12.71. MS (ES^+) 437 ($\text{M}^+ - 1$, 100%).

(3S) t-Butyl (7-(4-benzyloxyphenyl)carbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino [1,2-a][1,2,4]triazepine-4-carboxylate (262k), (83%) was obtained: $[\alpha]_{\text{D}}^{22} +42.3^\circ$. (c 0.11, CH_2Cl_2); IR (KBr) 3287, 2997, 2935, 1735, 1681, 1606, 1501, 1296, 1248, 1173, 1155. ^1H NMR (CDCl_3) δ 9.23 (1H, s), 7.73 (2H, d), 7.38 (5H, m), 6.85 (2H, d), 5.08 (1H, m), 5.02 (2H, s), 4.48 (1H, bd), 4.15-3.65 (3H, m), 2.96 (1H, m), 2.45-2.10 (2H, m), 1.88 (1H, m), 1.63 (2H, m), 1.48 (9H, s). M.S. (ES^+) 509 ($\text{M}^+ + 1$).

Compounds 263a-k were synthesized via methods used to prepare 212b-f.

(4S) 6,10-Dioxo-7-(2-naphthalenesulfonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263a), 348mg (94%) obtained as a white foamy solid: mp. $[\alpha]_{\text{D}}^{21} +171^\circ$ (c 0.056, CH_2Cl_2); IR (KBr) 3426, 3233, 2953, 1734, 1663, 1481, 1415, 1340, 1214, 1167, 1132, 1075, 668; ^1H NMR (CDCl_3) δ 8.44 (1H, s), 8.00-7.60 (7H, m), 4.85-4.83 (1H, m), 4.25-4.00 (1H, m), 4.07-3.90 (1H, m), 3.70-3.46 (2H, m), 2.38-2.30 (1H, m), 2.12-

- 662 -

2.01 (1H, m), 1.91-1.83 (1H, m), 1.46-1.26 (1H, m),
1.13-1.06 (1H, m), 0.90-0.77 (1H, m). MS (ES⁺) 431.

**(4S) 7-(Benzo[b]thiophene-2-carbonyl)amino-6,10-dioxo-
1,2,3,4,7,8,9,10-octahydro-6H-**

- 5 **pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid
(263b)**. 200mg (100%) was obtained as a white solid:
mp. 155°C; $[\alpha]_D^{20} +13^\circ$ (c 0.07, CH₂Cl₂); IR (KBr) 3431,
2935, 1734, 1663, 1531, 1435, 1292, 1177; ¹H NMR
(CDCl₃) δ 9.73 (1H, bs), 7.73-7.27 (5H, m), 5.35-5.25
10 (1H, m), 4.56-4.48 (1H, m), 4.05-3.65 (3H, m), 3.12-
3.00 (1H, m), 2.50-2.45 (1H, m), 2.30-2.20 (1H, m),
2.10-2.00 (1H, m), 1.75-1.61 (2H, m). MS (ES⁺) 401.

**(4S) 6,10-Dioxo-7-(3-methoxyphenylureido)-
1,2,3,4,7,8,9,10-octahydro-6H-**

- 15 **pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid
(263c)**, 216mg, (100+%) obtained as a colourless foam:
 $[\alpha]_D^{23} 32.5^\circ$ (c 0.1, CH₂Cl₂); IR (KBr) 3326, 1730,
1661, 1610, 1555, 1495, 1431, 1314, 1288, 1217, 1175,
1161; ¹H NMR (CDCl₃) δ 7.87 (1H, s), 7.58 (1H, s), 7.19
20 (2H, m), 6.82 (1H, m), 6.62 (1H, m), 5.21 (1H, m), 4.55
(1H, m), 3.76 (3H, s), 4.0-3.65 (4H, m), 2.85 (1H, m),
2.35 (2H, m), 1.75 (1H, m), 1.71 (2H, m).

**(4S) 6,10-Dioxo-7-(2-methoxyphenylureido)-
1,2,3,4,7,8,9,10-octahydro-6H-**

- 25 **pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid
(263d)**, (100+%) obtained as colourless foam: $[\alpha]_D^{24}$
 $+11.7^\circ$ (c 0.1, CH₂Cl₂); IR (KBr) 3394, 3325, 1666,
1603, 1543, 1490, 1463, 1438, 1329, 1311, 1292, 1249,
1214, 1176, 1119, 1024, 752; ¹H NMR (CDCl₃) δ 8.15 (1H,

- 663 -

m), 7.97 (2H, m), 7.15-6.84 (3H, m), 5.29 (1H, m), 4.62 (1H, m), 4.04-3.65 (4H, m), 3.89 (3H, s), 2.92 (1H, m), 2.50 (1H, m), 2.30 (1H, m), 2.10-1.75 (2H, m).

(4S) 6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylacetyl-amino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263e), obtained as a white foamy solid (117mg, 98%): mp. 109-14°C; $[\alpha]_D^{24} +82.6^\circ$ (c 0.06, CH₂Cl₂); IR (KBr) 3700-2250 (br), 3437, 3274, 2959, 1733, 1664, 1481, 1437, 1310, 1177; ¹H NMR (CDCl₃) δ 7.99 (1H, s), 7.40-7.15 (5H, m), 5.15-5.10 (1H, m), 5.25-4.70 (1H, bs), 4.50-4.35 (1H, m), 3.95-3.50 (3H, m), 3.61 (2H, s), 2.93-2.78 (1H, m), 2.40-2.20 (2H, m), 2.10-1.80 (1H, m), 1.80-1.60 (2H, m). Anal. Calcd for C₁₇H₂₀N₄O₅·1H₂O: C, 53.96; H, 5.86; N, 14.81. Found: C, 54.12; H, 5.50; N, 14.68. MS (ES⁺) 360 (M⁺, 21%), 359 (M⁺ - 1, 100), 196 (14), 182 (14), 111 (7).

(4S) 6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-(3-phenylureido)-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263f), obtained as a white foamy solid (199mg, 92%): mp. 149-52°C; $[\alpha]_D^{24} +92.0^\circ$ (c 0.01, CH₃OH); IR (KBr) 3700-2300 (br), 3319, 2956, 1726, 1664, 1600, 1548, 1500, 1444, 1313, 1238, 755; ¹H NMR (D₆-DMSO) δ 8.90 (1H, s), 8.24 (1H, s), 7.42 (2H, d), 7.30-7.20 (2H, m), 7.00-6.90 (1H, m), 4.98-4.92 (1H, m), 4.32-4.22 (1H, m), 3.80-3.55 (3H, m), 2.85-2.70 (1H, m), 2.30-2.20 (1H, m), 2.20-2.00 (1H, m), 1.90-1.35 (3H, m). Anal. Calcd for C₁₆H₁₉N₅O₅·0.75H₂O: C, 51.26; H, 5.51; N, 18.68. Found: C, 51.11; H, 5.23; N,

- 664 -

18.42. MS (ES^+) 361 (M^+ , 20%), 360 ($\text{M}^+ - 1$, 100), 241 (11), 240 (89), 196 (15), 175 (29), 111 (12).

(4S) 6,10-Dioxo-7-(indole-2-carboxamido)-
1,2,3,4,7,8,9,10-octahydro-6H-

- 5 pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid
(263g), was obtained as a white solid (259mg, 92%)mp.
248-51°C; $[\alpha]_{\text{D}}^{24} +94.0^\circ$ (c 0.01, CH_3OH); IR (KBr) 3700-
2300 (br) 3341, 2956, 1738, 1668, 1651, 1529, 1425,
1311, 1259, 751; ^1H NMR (D_6 -DMSO) δ 13.29 (1H, bs),
10 11.72 (1H, s), 10.64 (1H, s), 7.65 (1H, d), 7.45 (1H,
d), 7.26-7.15 (1H, m), 7.17 (1H, s), 7.10-7.00 (1H, m),
5.05-4.95 (1H, m), 4.40-4.25 (1H, m), 3.90-3.50 (3H,
m), 2.88-2.75 (1H, m), 2.38-2.20 (1H, m), 2.20-2.00
(1H, m), 1.90-1.35 (3H). Anal. Calcd for
15 $\text{C}_{18}\text{H}_{19}\text{N}_5\text{O}_5 \cdot 0.5\text{H}_2\text{O}$: C, 53.59; H, 5.25; N, 17.35. Found:
C, 53.66; H, 4.88; N, 17.11. MS (ES^+) 385 (M^+ , 23%),
384 ($\text{M}^+ - 1$, 100), 298 (6), 253 (8), 227 (10), 199
(23), 196 (10), 173 (9), 126 (21).

- (4S) 7-[(4-Acetamido)benzamido]-6,10-dioxo-
20 1,2,3,4,7,8,9,10-octahydro-6H-
pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid
(263h), was obtained as a white solid (282mg, 99%): mp.
210-5°C; $[\alpha]_{\text{D}}^{24} +74.5^\circ$ (c 0.01, CH_3OH); IR (KBr) 3700-
2300 (br) 3444, 3316, 2960, 1664, 1599, 1531, 1439,
25 1301, 1184; ^1H NMR (D_6 -DMSO) δ 13.30 (1H, bs), 10.50
(1H, s), 10.25 (1H, s), 7.80 (2H, d), 7.68 (2H, d),
5.00-4.90 (1H, m), 4.35-4.25 (1H, m), 3.90-3.40 (3H,
m), 2.88-2.70 (1H, m), 2.35-2.25 (1H, m), 2.25-1.95
(1H, m), 2.08 (3H, s), 1.95-1.35 (3H, m). MS (ES^+) 403

- 665 -

(M⁺, 10%), 402 (M⁺ - 1, 100), 358 (10), 247 (10), 227 (16), 219 (51), 198 (12), 184 (17).

(4S) 6,10-Dioxo-7-(4-methoxybenzoylamino)-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-carboxylic acid

5 **(263i)**, was obtained as a white glassy solid (approx 100%) used without purification: ¹H NMR (CDCl₃) δ 9.23 (1H, s), 7.72 (2H, d, J = 8.8), 6.81 (2H, d, J = 8.9), 5.22 (1H, m), 4.51 (1H, m), 3.97-3.72 (2H, m), 3.81 (3H, s), 3.03 (1H, m), 2.51-2.46 (1H, m), 2.31-2.25
10 (1H, m), 2.03 (1H, m), 1.72 (2H, m).

(4S) 6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylsulphonylamino-6H-

pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid

(263j), was obtained as a white solid (100%): mp. 73-
15 83°C (dec); [α]_D²² +104.7° (c 0.3, CH₂Cl₂); IR (KBr) 3600-2500 (br), 3208, 1734, 1666, 1481, 1448, 1416, 1338, 1311, 1214, 1171, 1091, 729, 689; ¹H NMR (CDCl₃) δ 7.87 (3H, m), 7.70-7.50 (3H, m), 7.16 (1H, brs), 4.99 (1H, m), 4.37 (1H, brd, J = 12.8), 3.92 (1H, m), 3.67
20 (2H, m), 2.36 (2H, m), 2.13 (1H, brd, J = 12.2), 1.56 (3H, m). Anal. Calcd for C₁₅H₁₈SN₄O₆•0.25CF₃CO₂H: C, 45.31; H, 4.48; N, 13.64. Found: C, 45.48; H, 4.71; N, 13.43. MS (ES⁺) 383 (MH⁺, 100%). Accurate mass calculated for C₁₅H₁₉SN₄O₆ (MH⁺): 383.1025. Found:
25 383.1007.

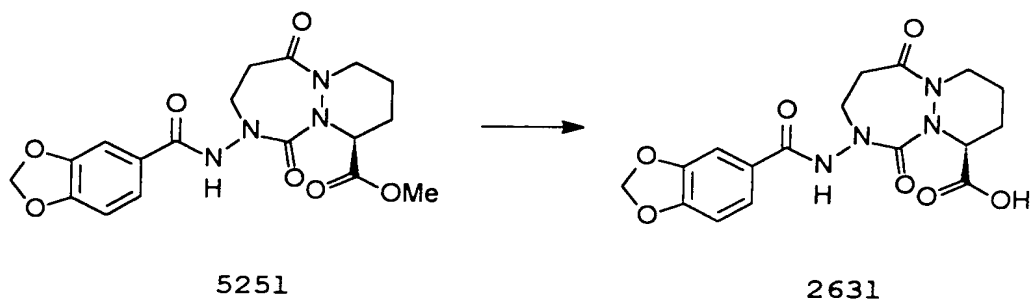
(4S) 7-(4-Benzyloxyphenyl)carbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-

pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid

(263k), (100%) obtained: mp. 130-142°C; IR (KBr) 3272,

- 666 -

2945, 1738, 1650, 1611, 1501, 1445, 1309, 1255, 1171;
 ^1H NMR (CDCl_3) δ 9.35 (1H, s), 7.74 (2H, d), 7.38 (5H,
 m), 6.85 (2H, d), 5.40 (1H, bs), 5.19 (1H, s), 5.02
 (2H, s), 4.49 (1H, d), 3.92 (2H, m), 3.68 (1H, m), 2.99
 5 (1H, bs), 2.43 (1H, bs), 2.22 (1H, bs), 1.99 (1H, bs),
 1.68 (2H, bs).

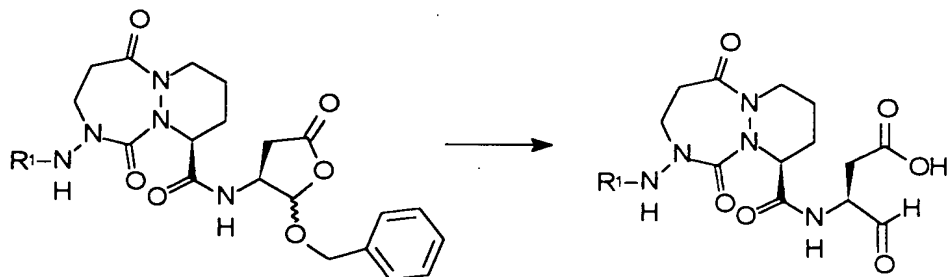


(4S) Methyl 6,10-dioxo-7-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-
 10 6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate
 (5251), was synthesized via method used to prepare 211
 to afford a white crystalline solid (3.35g, 83%): mp.
 214-5°C; $[\alpha]_D^{20} +75.2^\circ$ (c 0.1, CH_2Cl_2); IR (KBr) 3272,
 2955, 1747, 1664, 1610, 1485, 1443, 1265, 1040; ^1H NMR
 15 (CDCl_3) δ 8.66 (1H, s), 7.32 (1H, dd), 7.23 (1H, d),
 6.76 (1H, d), 6.02 (2H, s), 5.20 (1H, dd), 4.55-4.45
 (1H, m), 4.03-3.70 (3H, m), 3.78 (3H, s), 3.05-2.88
 (1H, m), 2.47-2.35 (1H, m), 2.35-2.20 (1H, m), 2.10-
 1.90 (1H, m), 1.85-1.50 (2H, m). Anal. Calcd for
 20 $\text{C}_{18}\text{H}_{20}\text{N}_4\text{O}_7 \cdot 0.5\text{H}_2\text{O}$: C, 52.87; H, 5.06; N, 13.70. Found:
 C, 52.84; H, 5.00; N, 13.66. MS (ES^+) 406 ($\text{M}^+ + 2$,
 20%), 405 ($\text{M}^+ + 1$, 100), 391 (10), 162 (6), 148 (3),
 105 (2).

(4S) 6,10-Dioxo-7-(3,4-methylenedioxybenzoylamino)-
 25 1,2,3,4,7,8,9,10-octahydro-6H-

- 667 -

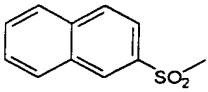
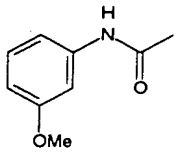
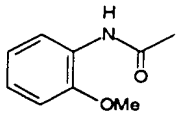
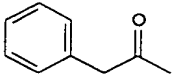
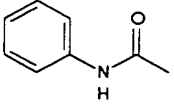
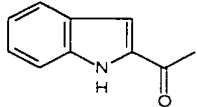
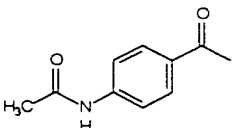
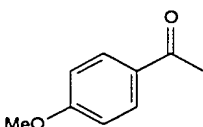
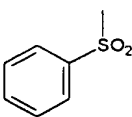
pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (2631). A suspension of 5251 (3.32g, 8.2mmol) in tetrahydrofuran (60ml) was treated with a solution of LiOH·H₂O (0.69g, 16.4mmol, 2.0 equiv) in water (20ml). The resulting mixture was stirred for 1h, concentrated and the residue dissolved in water (50ml). The solution was acidified using 2M. NaHSO₄ and the product extracted with EtOAc (100ml and 50ml portions). The combined extract was washed once with brine (2 x 50ml), dried (MgSO₄) and concentrated to afford 2631 as a white crystalline solid (2.87g, 90%): mp. 154-8°C; $[\alpha]_D^{20} +85.6^\circ$ (c 0.01, CH₃OH); IR (KBr) 3700-2300 (br), 3248, 2942, 1733, 1681, 1658, 1648, 1536, 1486, 1440, 1297, 1255, 1037; ¹H NMR (D₆-DMSO) δ 13.23 (1H, bs), 10.45 (1H, s), 7.45 (1H, d), 7.35 (1H, s), 7.03 (1H, d), 6.12 (2H, s), 5.00-4.93 (1H, m), 4.35-4.25 (1H, m), 3.90-3.40 (3H, m), 2.95-2.70 (1H, m), 2.40-2.25 (1H, m), 2.15-2.00 (1H, m), 1.91-1.40 (3H, m). Anal. Calcd for C₁₇H₁₈N₄O₇·0.8H₂O: C, 50.45; H, 4.88; N, 13.84. Found: C, 50.80; H, 4.95; N, 13.36. MS (ES⁺) 390 (M⁺, 19%), 389 (M⁺ - 1, 100), 345 (9), 204 (31), 182 (27), 111 (12).



264a, c-1

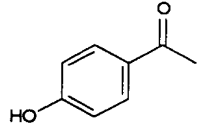
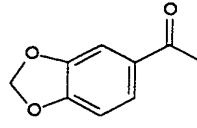
265a, c, d, f
1015, 1018, 1027,
1052, 1056, 1075, 1095

- 668 -

compound	R ¹
264a 265a	 <chem>CC(=O)S(=O)c1ccc2ccccc2c1</chem>
264c 265c	 <chem>CC(=O)Nc1ccc(OC)cc1</chem>
264d 265d	 <chem>CC(=O)Nc1ccccc1OC</chem>
264e 1095	 <chem>CC(=O)Cc1ccccc1</chem>
264f 265f	 <chem>CC(=O)Nc1ccccc1</chem>
264g 1075	 <chem>CC(=O)c1c[nH]c2ccccc12</chem>
264h 1018	 <chem>CC(=O)Nc1ccc(C(=O)C)cc1</chem>
264i 1052	 <chem>CC(=O)c1ccc(OC)cc1</chem>
264j 1027	 <chem>CS(=O)(=O)c1ccccc1</chem>

- 669 -

20

264k 1056	
264l 1015	

[4*S*(2*S*,3*S*)] N-(2-Benzyloxy-5-oxo-tetrahydrofuran-3-yl)-
 25 6,10-dioxo-7-(2-naphthalenesulfonyl)amino-
 1,2,3,4,7,8,9,10-octahydro-6H-
 pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide
 (264a), was synthesized by a similar method as compound
 213e to afford a white solid (240mg, 82%): IR (KBr)
 30 3380, 3066, 2947, 1789, 1750, 1691, 1454, 1417, 1368,
 1298, 1262, 1235, 1193, 1118, 756, 696; ¹H NMR (D₆-
 DMSO) δ 8.59 (1H, d, J = 6.8), 8.48 (1H, s), 8.25-8.09
 (3H, m), 7.85-7.75 (3H, m), 7.36 (5H, m), 5.39 (1H, m),
 4.21 (2H, AB, J = 14.2), 4.53-4.49 (1H, m), 4.25-4.10
 35 (2H, m), 3.65-3.44 (3H, m), 3.13-2.99 (1H, m), 2.43-
 2.16 (1H, m), 1.72-0.72 (7H, m). Anal. Calcd for
 C₃₀H₃₁N₅O₈S: C, 57.96; H, 5.03; N, 11.27. Found: C,
 57.28; H, 5.14; N, 10.48. MS (ES⁺) 622.

[4*S*(2*S*,3*S*)] N-(2-Benzyloxy-5-oxo-tetrahydrofuran-3-yl)-
 40 6,10-dioxo-7-(3-methoxyphenylureido)-1,2,3,4,7,8,9,10-
 octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-1-
 carboxamide (264c), was prepared by a similar method as
 213e, (55%) as a colourless foam: mp. 135-40°C; [α]_D²²
 +51.6° (c 0.1, CH₂Cl₂); IR (KBr) 3314, 1790, 1664,

- 670 -

1608, 1543, 1496, 1455, 1428, 1325, 1287, 1250, 1218, 1160, 1118; ^1H NMR (CDCl_3) δ 8.00 (1H, d, $J = 7.1$), 7.66 (1H, s), 7.55 (1H, s), 7.28 (5H, m), 7.14 (2H, m), 6.87 (1H, d, $J = 7.4$), 6.59 (1H, m), 5.42 (1H, s), 4.66 (5H, m), 3.90-3.65 (4H, m), 3.73 (3H, s), 2.98 (2H, m), 2.38 (2H, m), 2.01-1.65 (3H, m).

[4*S*(2*S*,3*S*)] *N*-(2-Benzoyloxy-5-oxo-tetrahydrofuran-3-yl)-6,10-dioxo-7-(2-methoxyphenylureido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2,4]triazepine-1-carboxamide (264d), was prepared by a similar method as 213e, (72%) as colourless foam: $[\alpha]_D^{22} +21.4^\circ$ (c 0.1, CH_2Cl_2); IR (KBr) 3302, 1791, 1689, 1678, 1664, 1602, 1536, 1489, 1461, 1437, 1420, 1249, 1119, 1023, 942, 751; ^1H NMR (CDCl_3) δ 8.07 (1H, d, $J = 7.7$), 7.82 (1H, s), 7.68 (1H, d, $J = 6.7$), 7.49 (1H, s), 7.34 (5H, m), 6.96 (3H, m), 5.47 (1H, s), 4.82 (2H, d + m, $J = 11.5$), 4.63 (1H, d, $J = 11.5$), 4.49 (2H, m), 3.85 (4H, s + m), 3.68 (2H, m), 3.01 (2H, m), 2.46 (2H, m), 1.95 (3H, m), 1.57 (1H, m).

[4*S*(2*RS*,3*S*)] *N*-(2-Benzoyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylacetyl-amino-6H-pyridazino[1,2-*a*][1,2,4]triazepine-4-carboxamide (264e) was synthesized via a similar method as used to prepare 213e to afford a mixture of diastereomers (Syn:anti isomer ratio 9:1) as a white glassy solid (128mg, 78%): mp. 103-8°C; IR (KBr) 3419, 3302, 1793, 1664, 1535, 1421, 1327, 1256, 1123, 973; ^1H NMR (D_6 -DMSO) δ 10.20 (0.9H, s), 9.35 (0.1H, s), 8.74 (0.1H, d), 8.49 (0.9H, d), 7.36-7.15 (10H, m), 5.67 (0.9H, d), 5.44 (0.1H, s),

- 671 -

4.85-4.75 (1H, m), 4.74-4.60 (1H, m), 4.77 and 4.63 (2H, dd), 4.30-4.10 (1H, m), 3.80-3.40 (3H, m), 3.43 (2H, s), 3.10-2.40 (3H, m), 2.25-2.15 (1H, m), 2.00-1.35 (4H, m). Anal. Calcd for $C_{28}H_{31}N_5O_7 \cdot 0.5H_2O$: C, 60.21; H, 5.77; N, 12.53. Found: C, 60.38; H, 5.83; N, 12.13. MS (ES^+) 551 ($M^+ + 2$, 33%), 550 ($M^+ + 1$, 100), 480 (7), 343 (8), 279 (4).

[4*S*(2*RS*,3*S*)] N-(2-Benzylloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-(3-phenylureido)-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264f), was prepared by a similar method as compound 213e to afford the pure syn-isomer as a white foamy solid (225mg, 82%): mp. 130-5°C; $[\alpha]_D^{24} +10.8^\circ$ (c 0.1, CH_2Cl_2); IR (KBr) 3316, 1791, 1688, 1676, 1664, 1601, 1536, 1445, 1314, 1242, 973; 1H NMR (D_6 -DMSO) δ 8.84 (1H, s), 8.49 (1H, d), 8.19 (1H, s), 7.45-7.18 (9H, m), 7.00-6.90 (1H, m), 5.68 (1H, d), 4.90-4.81 (1H, m), 4.75-4.60 (1H, m), 4.78 and 4.63 (2H, dd), 4.30-4.20 (1H, m), 3.75-3.55 (3H, m), 2.85-2.55 (3H, m), 2.25-2.15 (1H, m), 2.00-1.35 (4H, m). Anal. Calcd for $C_{27}H_{30}N_6O_7 \cdot 0.5H_2O$: C, 57.95; H, 5.58; N, 15.02. Found: C, 58.12; H, 5.64; N, 14.81. MS (ES^+) 552 ($M^+ + 2$, 30%), 551 ($M^+ + 1$, 100), 362 (19), 299 (10), 279 (4).

[4*S*(2*S*,3*S*)] N-(2-Benzylloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-7-(indole-2-carboxamido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264g), was prepared by a similar method as compound 213e to afford the pure anti-isomer as a white solid (284mg, 80%): mp. 148-53°C; $[\alpha]_D^{24} +72.0^\circ$ (c 0.1,

- 672 -

CH₂Cl₂); IR (KBr) 3404, 3295, 1789, 1660, 1536, 1421, 1310, 1260, 1122, 749; ¹H NMR (D₆-DMSO) δ 11.72 (1H, s), 10.58 (1H, s), 8.73 (1H, d), 7.65 (1H, d), 7.58-7.27 (6H, m), 7.27-7.10 (1H, m), 7.17 (1H, s), 7.10-7.00 (1H, m), 5.46 (1H, s), 4.90-4.85 (1H, m), 4.77 and 4.68 (2H, dd), 4.35-4.25 (2H, m), 3.95-3.55 (3H, m), 3.09 (1H, dd), 2.95-2.80 (1H, m), 2.47-2.25 (2H, m), 2.10-1.35 (4H, m). MS (ES⁺) 574 (M⁺, 35%), 573 (M⁺ - 1, 100), 384 (16), 383 (69), 341 (23), 327 (12), 267 (13), 200 (22).

[4*S*(2*RS*,3*S*)] 7-[(4-Acetamido)benzamido]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2,4]triazepine-4-carboxamide (264h), was prepared by a similar method as compound 213e to afford a mixture of diastereomers (Syn:anti isomer ratio 9:1) as a white solid (276mg, 70%): mp. 147-52°C; IR (KBr) 3444, 3304, 1793, 1665, 1602, 1531, 1505, 1423, 1294, 1264, 1181, 1123, 966; ¹H NMR (D₆-DMSO) δ 10.41 (1H, s), 10.22 (1H, s), 8.71 (0.1H, d), 8.48 (0.9H, d), 7.78 (2H, d), 7.67 (2H, d), 7.35-7.30 (5H, m), 5.68 (0.9H, d), 5.45 (0.1H, s), 4.88-4.80 (1H, m), 4.75-4.60 (1H, m), 4.77 and 4.63 (2H, dd), 4.30-4.20 (1H, m), 3.90-3.50 (3H, m), 3.10-2.50 (3H, m), 2.35-2.20 (1H, m), 2.07 (3H, s), 2.05-1.35 (4H, m). Anal. Calcd for C₂₉H₃₂N₆O₈•1H₂O: C, 57.04; H, 5.61; N, 13.76. Found: C, 56.79; H, 5.50; N, 13.53. MS (ES⁺) 594 (M⁺ + 2, 34%), 593 (M⁺ + 1, 100), 387 (8), 386 (38), 358 (8), 162 (19).

[4*S*(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-7-(4-methoxybenzoylamino)-octahydro-6H-pyridazino[1,2-*a*][1,2,4]triazepine-4-carboxamide

- 673 -

(264i), was prepared by a similar method to that described for compound 213e to afford a white solid (70%): mp. 116-118°C; IR (KBr) 3315, 2951, 1793, 1664, 1607, 1502, 1258, 1177; ¹H NMR (CDCl₃) δ 8.07 (1H, s),
 5 7.77 (2H, d, J = 8.6), 7.35 (5H, m), 6.94 (2H, d, J = 8.5), 6.74 (1H), 4.89 (1H, d, J = 11.1), 4.74 (1H, m), 4.60 (1H, d, J = 11.0), 4.48, 4.41 (1H, 2m), 3.86 (3H, s), 3.79, 3.71-3.53 (3H, 2m), 2.87 (2H, m), 2.44 (1H, m), 2.18, 1.91, 1.68 (5H, 3m).

10 [4S(2S,3S)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylsulphonylamino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264j), was synthesized by a similar method as compound
 15 213e to afford a foam (88%): [α]_D²⁴ +74.2° (c 0.36, CH₂Cl₂); IR (KBr) 3332, 3235, 1793, 1664, 1537, 1448, 1416, 1337, 1169, 118, 1092, 940, 690; ¹H NMR (CDCl₃) δ 7.99 (1H, s), 7.88 (2H, d, J = 6.8), 7.64-7.48 (3H, m), 7.34 (5H, s), 7.13 (1H, d, J = 6.9), 5.39 (1H, s), 4.81
 20 (2H, m), 4.62 (1H, d, J = 11.5), 4.48 (1H, m), 4.33 (1H, m), 3.85 (1H, m), 3.59 (2H, m), 3.03 (1H, dd, J = 7.6, 18.2), 2.49-2.28 (3H, m), 1.94-1.40 (4H, m).
 Anal. Calcd for C₂₆H₂₉SN₅O₈: C, 54.63; H, 5.11 N, 12.25. Found: C, 54.42; H, 5.28; N, 11.62. MS (ES⁺) 572 (MH⁺, 100%).
 25 Accurate mass calculated for C₂₆H₃₀SN₅O₈ (MH⁺): 572.1815. Found: 572.1802.

[4S(2RS,3S)] 7-(4-Benzyloxyphenyl)carbonylamino-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide
 30

- 674 -

(264k), was prepared by the method used for 213e (96%):
 IR (KBr) 3294, 2946, 1793, 1658, 1606, 1535, 1501,
 1248, 1174, 1119. ^1H NMR (CDCl_3) δ 8.91 (1H, s), 7.85
 (3H, m), 7.4 (10H, m), 7.02 (2H, d), 5.35 (1H, s), 5.10
 5 (2H, s), 4.8-4.3 (5H, m), 4.00 (1H, bs), 3.78 (2H, m),
 2.90 (2H, m), 2.5-1.5 (6H, m).

[4S(2RS,3S)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-
 6,10-dioxo-7-(3,4-methylenedioxybenzoylamino)-
 1,2,3,4,7,8,9,10-octahydro-6H-
 10 pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide
 (2641), was prepared by a similar method as compound
 213e to afford a mixture of diastereomers (syn:anti
 isomer ratio 1:1) as a white solid (1.72g, 71%): mp.
 148-60°C; IR (KBr) 3314, 1780, 1677, 1658, 1651, 1550,
 15 1485, 1439, 1258, 1132, 1038, 943; ^1H NMR (D_6 -DMSO) δ
 10.39 (1H, s), 8.71 (0.5H, d), 8.49 (0.5H, d), 7.44
 (1H, d), 7.42-7.30 (6H, m), 7.03 (1H, d), 6.12 (2H, s),
 5.68 (0.5H, d), 5.45 (0.5H, s), 4.90-4.82 (1H, m),
 4.82-4.58 (2.5H, m), 4.40-4.10 (1.5H, m), 3.90-3.65
 20 (2H, m), 3.65-3.43 (1H, m), 3.09 (0.5H, dd), 2.90-2.55
 (1.5H, m), 2.45-2.10 (2H, m), 2.10-1.35 (4H, m). Anal.
 Calcd for $\text{C}_{28}\text{H}_{29}\text{N}_5\text{O}_9 \cdot 0.2\text{H}_2\text{O}$: C, 57.67; H, 5.08; N,
 12.01. Found: C, 58.01; H, 5.33; N, 11.51. MS (ES^+)
 581 ($\text{M}^+ + 2$, 33%), 580 (M^+ , 100), 374 (9), 373 (48),
 25 345 (12), 261 (4), 239 (7), 149 (9).

[3S(4S)] 3-[6,10-Dioxo-7-(2-naphthalenesulfonyl)amino-
 1,2,3,4,7,8,9,10-octahydro-6H-
 pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-
 oxobutanoic acid (265a), was prepared by a similar
 30 method as compound 265 to afford a white solid (37mg,

- 675 -

17%): mp. 126-30°C (dec); $[\alpha]_D^{20} +30^\circ$ (c 0.05, MeOH); IR (KBr) 3371, 2935, 1785, 1663, 1538, 1418, 1339, 1164, 669; ^1H NMR (CD_3OD) δ 8.44 (1H, s), 8.06-7.50 (7H, m), 7.22 (1H, d, $J = 8.4$), 4.58-4.57 (1H, m), 4.46-4.42 (1H, m), 4.16-4.09 (2H, m), 3.85-3.50 (3H, m), 2.84-2.78 (1H, m), 2.64-2.51 (1H, m), 2.44-2.15 (2H, m), 1.81-0.89 (4H, m). Anal. Calcd for $\text{C}_{23}\text{H}_{25}\text{N}_5\text{O}_8\text{S}\cdot\text{H}_2\text{O}$: C, 50.27; H, 4.95; N, 12.74. Found: C, 50.33; H, 5.04; N, 12.60. MS (ES^+) 530.

10 **[3S(4S)] 3-[6,10-Dioxo-7-(3-methoxyphenylureido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (265c)**, was prepared by a similar method as 265, (90%) as a colourless solid: mp. ~150°C
 15 (decomp.); $[\alpha]_D^{23} +94.8^\circ$ (c 0.1, 20% MeOH/ CH_2Cl_2); IR (KBr) 3330, 1780, 1660, 1610, 1550, 1495, 1428, 1326, 1287, 1251, 1223, 1160; ^1H NMR (CD_3OD) δ 7.16 (2H, m), 6.89 (1H, d, $J = 7.8$), 4.58 (1H, m), 4.37 (2H, m), 3.76 (6H, s + m), 2.95 (1H, m), 2.67 (1H, m), 2.33 (1H, m),
 20 2.20-1.85 (3H, m), 1.66 (1H, m).

[3S(4S)] 3-[6,10-Dioxo-7-(2-methoxyphenylureido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (265d), was prepared by a similar method as 265, (85%) as a
 25 colourless solid: mp. ~176-85°C; $[\alpha]_D^{23} +11.0^\circ$ (c 0.1, MeOH); IR (KBr) 3392, 3328, 1784w, 1665, 1603, 1537, 1490, 1462, 1437, 1337, 1290, 1290, 1217, 1177, 1119, 1023; ^1H NMR (CD_3OD) δ 8.02 (2H, m), 6.95 (4H, m), 5.05 (1H, m), 4.60 (2H, m), 3.92 (4H, s + m), 3.00 (2H, m),
 30 2.68 (1H, m), 2.39 (1H, m), 2.00 (4H, m), 1.69 (1H, m).

- 676 -

[3S(4S)] 3-(6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylacetamino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido)-4-oxobutanoic acid (1095), was prepared by a similar method as compound 265 to afford a white solid (84mg, 90%): mp. 180-6°C; $[\alpha]_D^{22} +22.3^\circ$ (c 0.065, CH₃OH); IR (KBr) 3700-2300 (br), 3287, 1664, 1536, 1425, 1261, 1181; ¹H NMR (CD₃OD) δ 7.35-7.20 (5H, m), 5.00-4.90 (1H, m), 4.60-4.50 (1H, m), 4.50-4.10 (2H, m), 3.90-3.50 (3H, m), 3.54 (2H, s), 3.00-2.80 (1H, m), 2.80-2.40 (2H, m), 2.35-2.20 (1H, m), 2.20-1.50 (4H, m). MS (ES⁺) 459 (M⁺ 24%), 458 (M⁺ - 1, 100), 358 (27), 175 (9), 149 (7), 137 (12). Accurate mass calculated for C₂₁H₂₆N₅O₇ (MH⁺): 460.1832. found: 460.1840.

[3S(4S)] 3-[6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-(3-phenylureido)-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (265f), was prepared by a similar method as compound 265 to afford a white foamy solid (130mg, 88%): mp. 157-62°C; $[\alpha]_D^{24} +41.7^\circ$ (c 0.1, CH₃OH); IR (KBr) 3700-2300 (br), 3325, 1782, 1663, 1547, 1443, 1315, 1242, 1181; ¹H NMR (CD₃OD) δ 7.40 (2H, dd), 7.35-7.20 (2H, m), 7.06-6.95 (1H, m), 5.05-4.95 (1H, m), 4.64-4.54 (1H, m), 4.50-4.35 (1H, m), 4.35-4.15 (1H, m), 3.90-3.69 (3H, m), 3.00-2.85 (1H, m), 2.80-2.45 (3H, m), 3.40-1.50 (4H, m). MS (ES⁺) 460 (M⁺, 24%), 459 (M⁺ - 1, 100), 341 (9), 340 (54), 296 (6), 239 (9).

[3S(4S)] 3-[6,10-Dioxo-7-(indole-2-carboxamido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-

- 677 -

oxobutanoic acid (1075), was prepared by a similar method as compound 265 to afford a white solid (184mg, 83%): mp. 210-5°C; $[\alpha]_D^{24} +43.9^\circ$ (c 0.1, CH₃OH); IR (KBr) 3700-2300 (br), 3309, 1660, 1537, 1423, 1311, 1262, 1184; ¹H NMR (CD₃OD) δ 7.61 (1H, d), 7.45 (1H, d), 7.28-7.15 (1H, m), 7.15-7.00 (1H, m), 7.13 (1H, s), 5.12-4.96 (1H, m), 4.62-4.55 (1H, m), 4.50-4.25 (2H, m), 4.00-3.69 (3H, m), 3.05-2.90 (1H, m), 2.80-2.30 (3H, m), 2.25-1.50 (4H, m). MS (ES⁺) 484 (M⁺, 26%), 483 (M⁺ - 1, 100), 383 (25), 245 (12), 208 (11), 200 (21), 174 (31), 137 (18).

[3S(4S)] 3-{7-[(4-Acetamido)benzamido]-6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]-triazepine-4-carboxamido}-4-oxobutanoic acid (1018), was prepared by a similar method as compound 265 to afford a white solid (177mg, 82%): mp. 235-40°C; $[\alpha]_D^{23} +27.3^\circ$ (c 0.1, CH₃OH); IR (KBr) 3700-2300 (br), 3311, 2957, 1662, 1599, 1531, 1318, 1266, 1182; ¹H NMR (CD₃OD) δ 7.83 (2H, d), 7.69 (2H, d), 5.10-4.95 (1H, m), 4.64-4.55 (1H, m), 4.50-4.35 (1H, m), 4.32-4.22 (1H, m), 4.00-3.65 (3H, m), 3.05-2.90 (1H, m), 2.80-2.30 (3H, m), 2.15 (3H, s), 2.15-1.50 (4H, m). Anal. Calcd for C₂₂H₂₆N₆O₈•1.5H₂O: C, 49.90; H, 5.52; N, 15.87. Found: C, 50.21; H, 5.41; N, 15.49. MS (ES⁺) 502 (M⁺, 28%), 501 (M⁺ - 1, 100), 401 (8), 218 (4), 119 (2), 118 (5), 113 (16).

[3S(4S)] 3-[6,10-Dioxo-7-(4-methoxybenzoylamino)-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (1052), was synthesized via method used to prepare 265 to afford a white solid

- 678 -

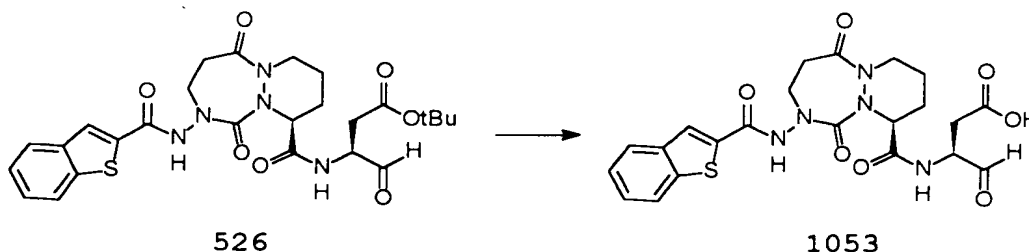
(0.194g, 100%): mp. 138-142°C; $[\alpha]_D^{20} +36.3^\circ$ (c 0.19, CH₃OH); IR (KBr) 3434-2962, 1782, 1660, 1607, 1537, 1504, 1441, 1424, 1313, 1293, 1258, 1177; ¹H NMR (CD₃OD) δ 7.11 (2H, d, J = 8.8), 6.90 (2H, d, J = 8.9),
 5 4.48 (1H, m), 4.34, 4.28 (1H, 2m), 4.15 (1H, m), 3.75 (3H, s), 3.75, 3.70 (3H, m), 2.88, 2.49, 2.28, 2.23, 2.00, 1.86, 1.79, 1.58 (8H, m).

[3S(4S)] 3-(6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylsulphonylamino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido)-4-oxobutanoic acid (1027), was synthesized by a similar method as compound 265 to afford a white foam (88%):
 $[\alpha]_D^{24} +22.6^\circ$ (c 0.17, MeOH); IR (KBr) 3349, 1789, 1663, 1537, 1448, 1337, 1169, 1092, 690; ¹H NMR (CD₃OD)
 15 δ 7.82 (2H, d, J = 7.8), 7.57 (3H, m), 4.74 (1H, m), 4.47 (1H, m), 4.24-4.10 (2H, m), 3.72-3.47 (4H, m), 2.62-2.48 (3H, m), 2.20 (1H, m), 1.94-1.35 (3H, m). MS (ES⁺) 480 (M⁺ - 1, 100%). Accurate mass calculated for C₁₉H₂₄SN₅O₈ (MH⁺): 482.1346. Found: 482.1325.

[3S(4S)] 3-[6,10-Dioxo-7-(4-hydroxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (1056), was prepared by the method used for 265 (95%): mp. >300°C; IR (KBr) 3392, 1660,
 25 1610, 1507, 1442, 1280, 1171, 1149, 1133. ¹H NMR (CD₃OD) δ 7.74 (2H, d J = 8.7), 6.84 (2H, d J = 8.7) 4.58 (1H, m), 4.41 (1H, bd, J = 12.6), 4.28 (1H, m), 3.85 (3H, m), 2.98 (1H, m), 2.8-2.3 (3H, m), 2.3-1.6 (4H, m).

- 679 -

[3*S*(4*S*)] 3-[6,10-Dioxo-7-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino[1,2-*a*][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (1015), was prepared by a similar
 5 method as used for 265 to afford a white solid (142mg, 58%): mp. 170-5°C; $[\alpha]_D^{25} +32.7^\circ$ (c 0.1, CH₃OH); IR (KBr) 3700-2500 (br), 3325, 2969, 1784, 1662, 1485, 1440, 1292, 1258, 1037; ¹H NMR (CD₃OD) δ 7.45 (1H, dd), 7.32 (1H, d), 6.90 (1H, d), 6.05 (2H, s), 5.10-4.90
 10 (1H, m), 4.62-4.54 (1H, m), 4.45-4.35 (1H, m), 4.33-4.22 (1H, m), 3.95-3.65 (3H, m), 3.05-2.90 (1H, m), 2.80-2.30 (3H, m), 2.20-1.50 (4H, m).



[3*S*(4*S*)] *t*-Butyl 3-[7-(benzo[*b*]thiophene-2-carbonyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino[1,2-*a*][1,2,4]triazepine]-4-oxobutanoate
 15 semicarbazone (526), was prepared by a similar method as used for 502 to afford a glassy solid: $[\alpha]_D^{20} +34^\circ$ (c 0.13, CH₂Cl₂); IR (KBr) 3437, 2929, 1670, 1530, 1428, 1288, 1156; ¹H NMR (CDCl₃) δ 10.0 (1H, bs), 9.74
 20 (1H, bs), 7.93 (1H, s), 7.80-7.60 (2H, m), 7.40-7.18 (3H, m), 6.15-5.30 (2H, bs), 5.00-4.85 (2H, m), 4.50-4.25 (1H, m), 3.95-3.75 (3H, m), 3.12-2.78 (2H, m), 2.73-1.60 (7H, m), 1.36 (9H, s). Anal. Calcd for

- 680 -

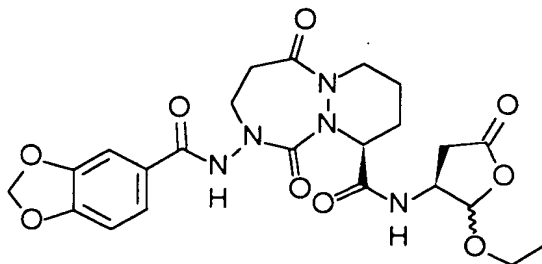
$C_{27}H_{34}N_8O_7S$: C, 52.76; H, 5.58; N, 18.23. Found: C, 52.25; H, 5.74; N, 16.30. MS (ES^+) 615.

[3*S*(4*S*)] 3-[7-(Benzo[*b*]thiophene-2-carbonyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-

5 pyridazino[1,2-*a*][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (1053), was prepared by a similar

method as used for 214 to afford a white solid (106mg, 73%): $[\alpha]_D^{20} +22^\circ$ (c 0.10, MeOH); IR (KBr) 3428, 2944, 1733, 1652, 1532, 1433, 1337, 1288, 1186; 1H NMR

10 (CD₃OD) δ 7.95 (1*H*, s), 7.90-7.85 (2*H*, m), 7.43-7.35 (2*H*, m), 4.98 (1*H*, m), 4.65-4.52 (1*H*, m), 4.40-4.20 (2*H*, m), 3.85-3.70 (3*H*, m), 3.30-3.25 (3*H*, m), 3.03-2.85 (1*H*, m), 2.70-2.31 (3*H*, m), 2.10-1.55 (4*H*, m). MS (ES^+) 500 (as methyl acetal of the aldehyde).



15

528

[4*S*(2*RS*,3*S*)] 6,10-Dioxo-*N*-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-7-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino[1,2-*a*][1,2,4]triazepine-4-carboxamide

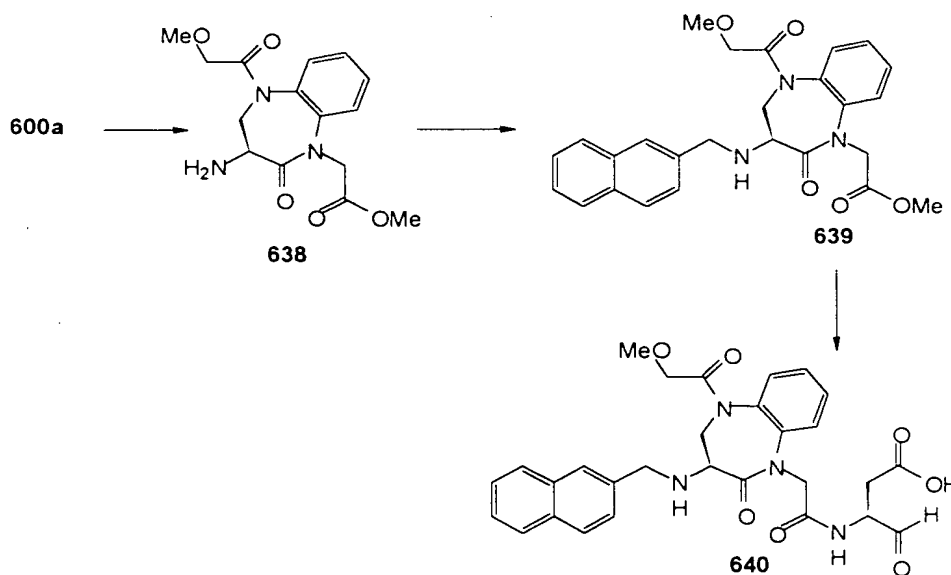
20 (528), was prepared by a similar method as compound 213e to afford a mixture of diastereomers (Syn: anti isomer ratio 1:1) as a creamy white foamy solid (1.05g,

- 681 -

58%): mp. 124-32°C; IR (KBr) 3312, 2979, 1790, 1664, 1610, 1532, 1485, 1285, 1120, 1037, 932; ^1H NMR (D_6 -DMSO) δ 10.39 (1H, s), 8.71 (0.5H, d), 8.43 (0.5H, d), 7.45 (1H, d), 7.36 (1H, s), 7.04 (1H, d), 6.12 (2H, s), 5.58 (0.5H, d), 5.34 (0.5H, s), 4.95-4.85 (1H, m), 4.70-4.52 (0.5H, m), 4.35-4.10 (1.5H, m), 3.95-3.50 (5H, m), 3.03 (0.5H, dd), 2.90-2.55 (1.5H, m), 2.46-2.20 (2H, m), 2.10-2.40 (4H, m), 1.16-1.13 (3H, 2 x t). Anal. Calcd for $\text{C}_{23}\text{H}_{27}\text{N}_5\text{O}_9 \cdot 0.6\text{H}_2\text{O}$: C, 52.29; H, 5.38; N, 13.26. Found: C, 52.53; H, 5.35; N, 12.78. MS (ES^+) 519 ($\text{M}^+ + 2$, 27%), 518 ($\text{M}^+ + 1$, 100), 472 (7), 374 (12), 373 (53), 345 (14), 149 (12).

Example 31

Compounds 640, 642, 645, 650, 653, 655, 656, 662, 668, 669, 670, 671, 677, 678, 681, 682, 683, 684, 686, 688a, 688b, 6891, 689b, 690a, 690b, 691a, 691b, 695a, 695b, 695c, 692a, 692b, 693 and 694 were prepared as follows.



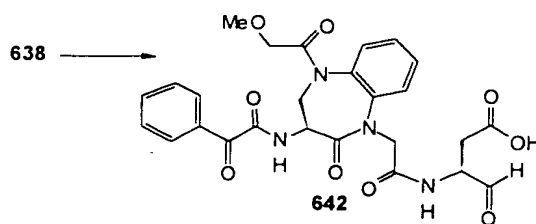
- 682 -

(3S)-2-Oxo-3-amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (638), was synthesized from 600a by methods similar to those used for making 602m from 600a to afford 2.4g of 638 as
5 a white solid.

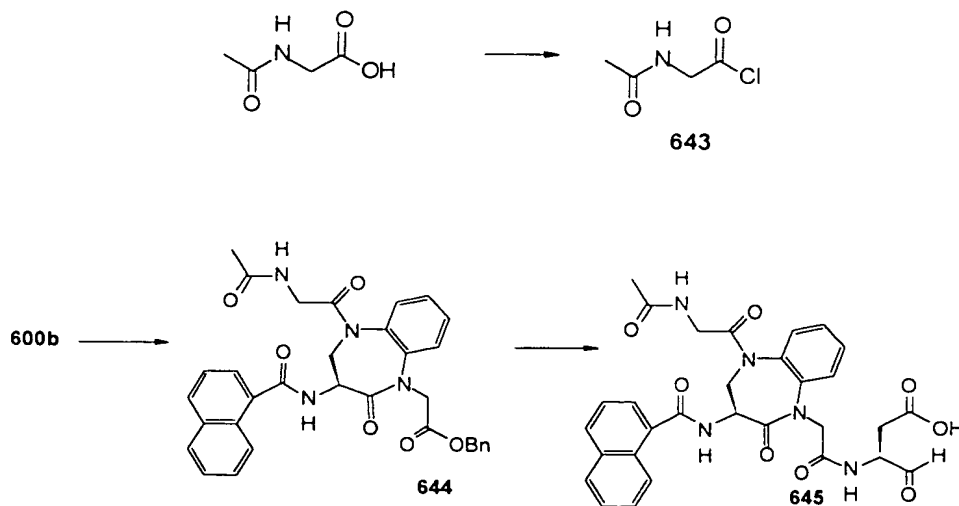
(3S)-2-Oxo-3-(2-naphthylmethylene)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (639). To a solution of 638 (630 mg, 1.76 mmol) and 2-naphthylmethyl bromide (428
10 mg, 1.94 mmol) in CH₃CN was added K₂CO₃ (608 mg, 4.4 mmol). The resulting mixture was stirred at ambient temperature. After 18 hours, the reaction mixture was diluted with CH₂Cl₂, washed with water then brine, dried over Na₂SO₄ then concentrated in vacuo. Flash
15 chromatography (SiO₂, 0 to 20% EtOAc/CH₂Cl₂) afforded 450mg of 639.

(3S)-3-[(3S)-2-Oxo-3-(2-naphthylmethylene)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyric acid (640), was synthesized
20 by methods used to make 605v from 602v to afford 205 mg of 640 as a white solid, ¹H NMR (CDCl₃) δ 2.4-2.55(m, 1H), 2.65-2.8(m, 1H), 3.2(s, 3H), 3.72-3.78(m, 1H),
3.85-4.0(m, 2H), 4.22-4.28(d, 1H), 4.26-4.5(m, 4H), 4.58-4.75(m, 1H), 4.78-4.85(m, 1H), 5.0-5.08(t, 1H),
25 7.35-7.65(m, 7H), 7.85-8.02(m, 4H).

- 683 -



(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylformylamino-5-methoxyacetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetylamino]4-oxo-butyrac acid (**642**), was synthesized from **638** by similar methods used to make **605m** to afford 213 mg of **642**, ^1H NMR (CD_3OD) δ 2.5(m, 1H), 2.68(ddd, 1H), 3.25(s, 2H), 3.3(s, 3H), 3.78(m, 2H), 4.0(d, 1H), 4.3(m, 1H), 4.6(m, 2H), 4.85(br. s, 2H), 7.08-7.22(m, 2H), 7.35(m, 1H), 7.4-7.65(m, 4H), 7.7(dd, 1H), 8.1(dd, 1H).



2-Acetamido-acetyl chloride (**643**). To a suspension of N-acetyl glycine (200 mg, 1.7 mmol) in CH_2Cl_2 (2.5 mLs) containing DMF (0.005 mLs) was added oxalyl chloride

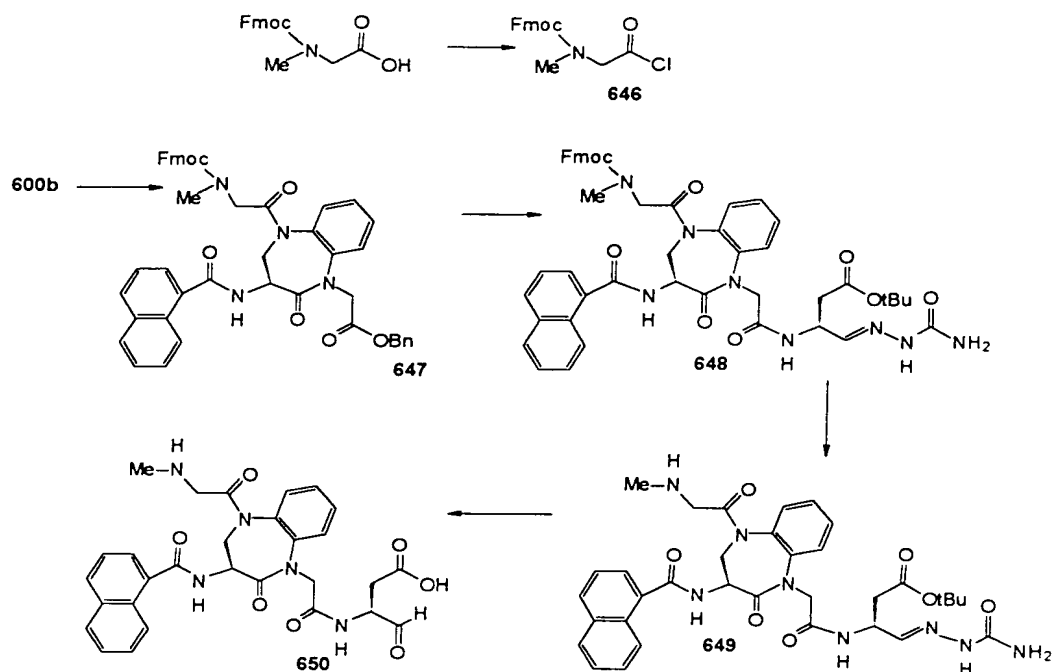
- 684 -

(0.450 mLs, 5.1 mmol). After stirring 30 minutes at ambient temperature, the mixture was concentrated to afford **643** as a crude product.

(3S)-2-Oxo-3-(1-naphthoyl)amino-5-(2-acetamido)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (644), was synthesized from **600b** by methods used to make **602d** from **600b** using **643** to afford 112 mg of **644**.

(3S)-3-[(3S)-2-Oxo-3-(1-naphthoyl)amino-5-(2-acetamido)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (645), was synthesized from **644** by methods used to make **605d** from **602d** to afford 43 mg of **645** as a white solid, ¹H NMR (CD₃OD) δ 1.95(s, 3H), 2.4(m, 1H), 2.65(m, 1H), 3.4(s, 1H), 3.55(m, 1H), 3.85(m, 1H), 4.05(d, 1H), 4.3(m, 1H), 4.4-4.6(m, 2H), 5.0(m, 1H), 7.4-7.7(m, 6H), 7.85-8.0(m, 2H).

- 685 -



2-(*N*-Methyl, *N*-fluorenylmethoxycarbonyl)aminoacetyl chloride (646), was prepared from *N*-Fmoc-sarcosine by method used to make 643 to afford 646 as a crude product.

- 5 (3*S*)-2-Oxo-3-(1-naphthoyl)amino-5-[2-(*N*-methyl, *N*-fluorenylmethoxycarbonyl)amino]acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid benzyl ester (647), was synthesized from 600b by methods used to synthesize 602d from 600b, using 646 to afford 481
- 10 mg of 647.

(3*S*)-3-[(3*S*)-2-Oxo-3-(1-naphthoyl)amino-5-[2-(*N*-methyl, *N*-fluorenylmethoxycarbonyl)amino]acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetyl]amino-4-oxo-butanoic acid *tert*-butyl ester semicarbazone (648), was

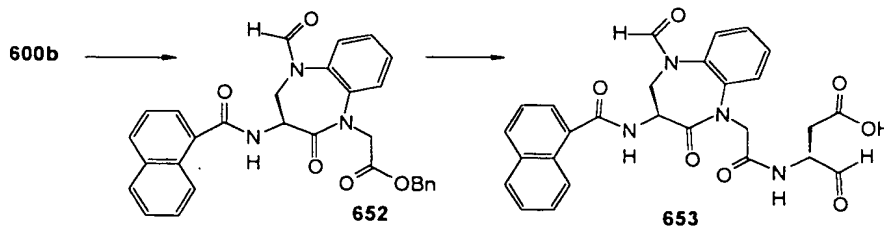
- 686 -

synthesized from **647** by methods used to prepare **604d** from **602d** to afford 409 mg of **648**.

(3S)-3-[(3S)-2-Oxo-3-(1-naphthoyl)amino-5-(2-methylamino) acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyric acid tert-butyl ester semicarbazone (649).

A solution of **648** (409 mg, 0.465 mmol) in MeCN:Et₂NH (4:1, v/v) was stirred at ambient temperature. After 45 minutes, the reaction mixture was concentrated *in vacuo*. Flash chromatography (SiO₂, 5% to 20% MeOH in CH₂Cl₂) afforded 241 mg of **649**.

(3S)-3-[(3S)-2-Oxo-3-(1-naphthoyl)amino-5-(2-methylamino) acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyric acid (650), was synthesized from **649** by methods used to prepare **605d** from **604** to afford 179 mg of **650** as a white solid, ¹H NMR (CD₃OD) δ 2.4-2.6(m, 2H), 2.7(s, 3H), 3.5(q, 1H), 3.8(m, 2H), 4.2-4.4(m, 2H), 4.3-4.45(m, 1H), 5.0-5.1(m, 2H), 7.4-7.7(m, 6H), 7.85-7.9(m, 2H), 8.2(m, 1H).

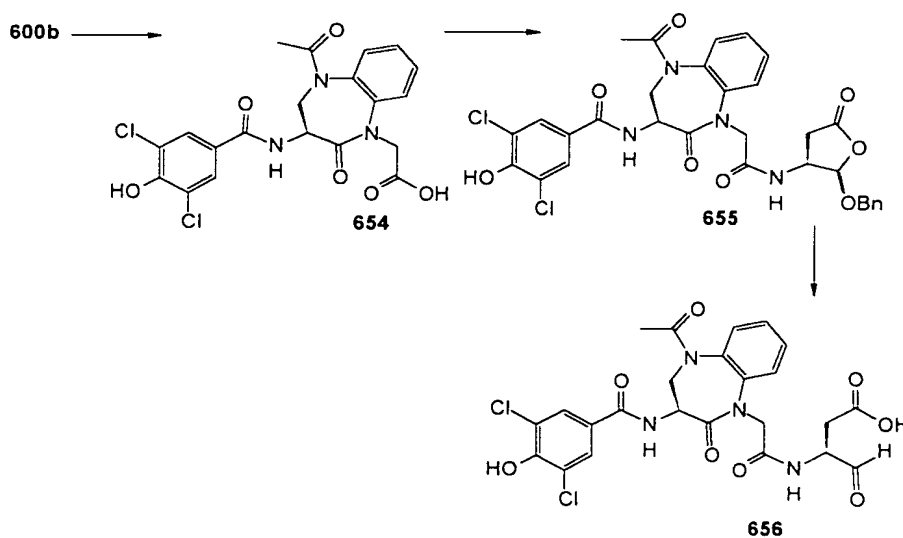


(3S)-2-Oxo-3-(1-naphthoyl)amino-5-formyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (652), was synthesized from **600b** by methods similar to those used to make **602n** from **600b**, using the

- 687 -

reagent obtained from reacting DMF with 3 equiv. of oxalyl chloride in a CH_2Cl_2 solution as R^3X , to afford 404 mg of **652**.

(3*S*)-3-[(3*S*)-2-Oxo-3-(1-naphthoyl)amino-5-formyl-
 5 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (**653**), was synthesized from **652** by methods used to prepare **605d** from **602d** to afford 84 mg of **653** as a white solid, ^1H NMR (CD_3OD) δ 2.3(m, 1H), 2.55(dd, 1H), 3.75(br. s, 1H), 4.25-4.6(m
 10 5H), 5.15(m, 1H), 7.2-7.45(m, 6H), 7.8-7.9(dd, 3H), 8.1(s, 1H), 8.2(m, 2H).



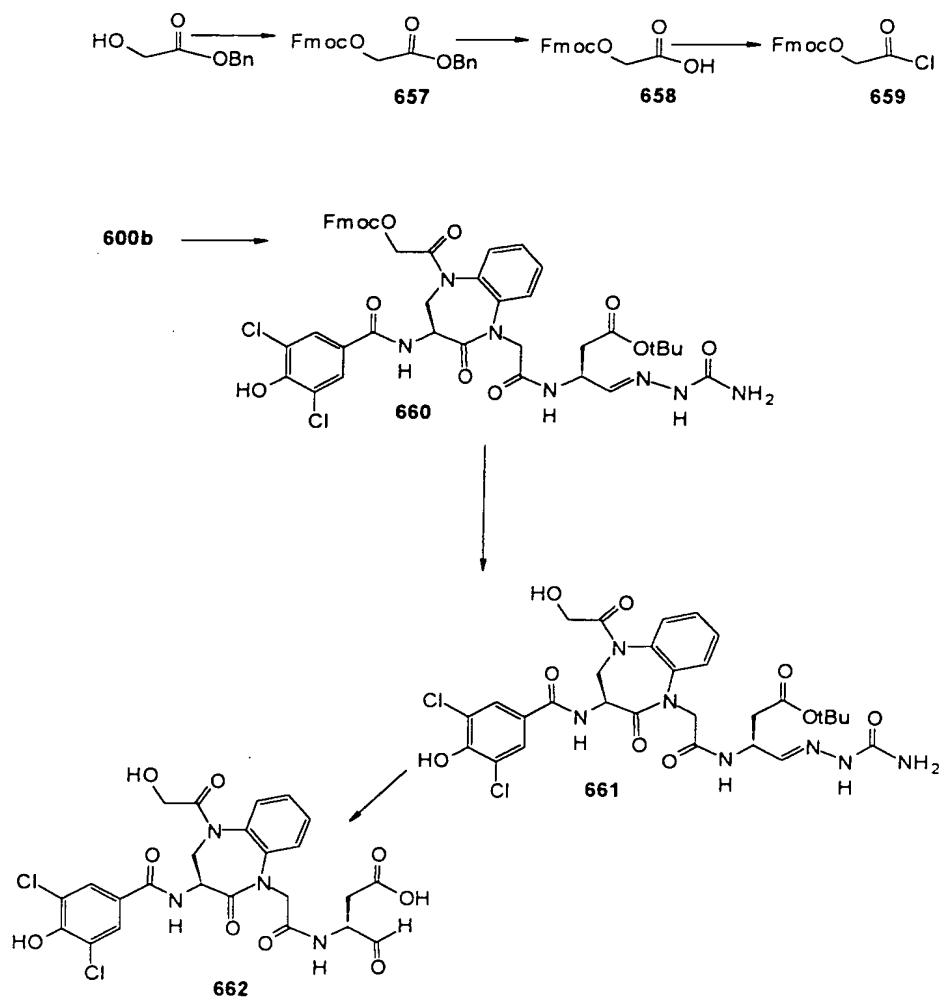
(3*S*)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid (**654**), was synthesized from **600b** using
 15 methods similar to those used for preparing **603d** from **600b** to afford 775 mg of **654**.

- 688 -

(3*S*)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-acetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetamide (655), was synthesized from 654 using the
5 method used to prepare 213e to afford 304 mg of 655, ¹H NMR (CD₃OD) δ 2.4(d, 1H), 2.6-2.75(m, 2H), 3.0(m, 1H), 3.45(m, 1H), 3.8(d, 1H), 4.0(t, 2H), 4.4(m, 2H), 4.5-4.55(m, 2H), 7.2-7.45(m, 4H), 7.85(s, 2H).

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dichloro, 4-hydroxybenzoyl)amino-5-acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (656), was synthesized from 655 using a method similar to that used to prepare 2002 from 2001 to afford 136 mg of 656 as a white solid, ¹H NMR (CD₃OD) δ 1.85(s, 3H),
10 2.5(m, 1H), 2.65(m, 1H), 3.7(m, 1H), 4.3(m, 1H),
15 4.55(m, 2H), 7.4-7.6(m, 4H), 7.85(s, 2H).

- 689 -



- 690 -

2-(Fluorenylmethoxycarbonyl)hydroxyacetic acid benzyl ester (657). To a solution of benzyl glycolate (6.0 g, 36.1 mmol) in CH_2Cl_2 , cooled via ice-water bath, was added fluorenylmethoxy chloroformate (14 g, 1.5 equiv.) then diisopropylethylamine (9 mLs, 1.5 equiv.). After 1 hour, reaction mixture was poured into a saturated aqueous solution of ammonium chloride and extracted with CH_2Cl_2 , dried over Na_2SO_4 then concentrated *in vacuo*. The product was triturated from MeOH to obtain 2.2 g of 657 as a first crop of white solid.

2-(Fluorenylmethoxycarbonate) acetic acid (658). To a solution of 657 (2.2 g, 5.93 mmol) in tetrahydrofuran was added 5% Pd/C (220 mg). The resulting suspension was vigorously stirred under hydrogen atmosphere. After 90 min, the reaction mixture was filtered through Celite. The filtrate was poured into saturated aqueous NaHCO_3 and washed twice with EtOAc. The aqueous layer was then acidified and the product extracted twice with CH_2Cl_2 , dried over Na_2SO_4 and concentrated *in vacuo* to afford 1.46 g (88%) of 658 as a white solid.

2-(Fluorenylmethoxycarbonate) acetyl chloride (659), was prepared from 658 by the method used to prepare 643 to afford 659 as a crude product.

(3S)-3-[(3S)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-(2-fluorenylmethoxycarbonate)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyric acid tert-butyl ester semicarbazone (660), was synthesized

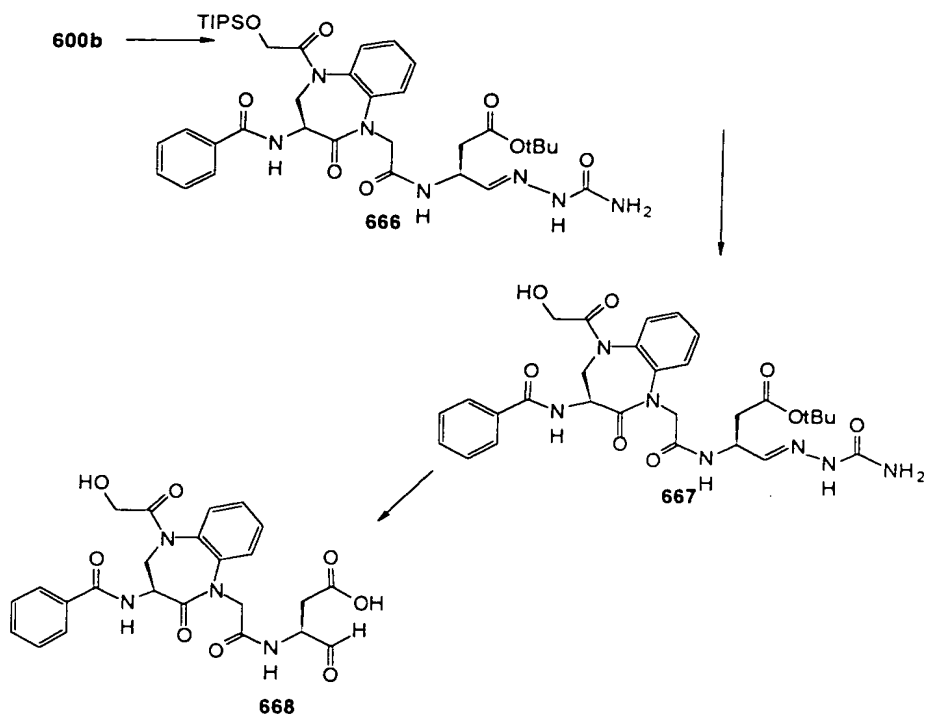
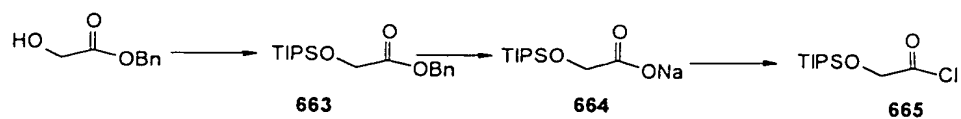
- 691 -

from 600b, using 659, by methods used to prepare 604d from 600b to afford 453 mg of 660.

(3S)-3-[(3S)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-(2-hydroxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyrac acid tert-butyl ester semicarbazone (661). A solution of 660 (423 mg) in MeOH:Et₂NH (1:1, v/v) was stirred at ambient temperature. After 10 minutes, the reaction mixture was concentrated *in vacuo* to a small volume. Precipitation by the addition of ether afforded 230 mg of 661.

(3S)-3-[(3S)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-(2-hydroxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyrac acid (662), was synthesized from 661 by the methods used to prepare 605d from 604 to afford 37 mg of 662 as a white solid, ¹H NMR (CD₃OD) δ 2.45(m, 1H), 2.7(m, 1H), 3.75(m, 1H), 3.9(d, 1H), 4.15(d, 1H), 4.35(m, 1H), 4.5(t, 2H), 4.7(dd, 1H), 7.4-7.6(m, 4H), 7.85(s, 2H).

- 692 -



- 693 -

2-(Triisopropylsilyloxy)acetic acid benzyl ester (663).

To a solution of benzyl glycolate (46.91g, 0.282 mol) and diisopropylethylamine (74 mLs, 0.423 mol) in CH₂Cl₂, cooled via water bath, was added a solution of
5 TIPSOTf (95 g, 0.31 mol) in CH₂Cl₂. The resulting mixture was allowed to warm to ambient temperature then poured into water, washed twice with 10% aqueous NaHSO₄, dried over Na₂SO₄ and concentrated *in vacuo*. Flash chromatography (SiO₂, 0 to 5% EtOAc in hexanes)
10 afforded 71.6 g of **663**.

2-(Triisopropylsilyloxy)acetic acid (664).

To a solution of **663** (0.4 g, 1.2 mmol) in EtOAc was added 10% Pd/C (33 mg). The resulting suspension was stirred under hydrogen atmosphere. After 15 hours, the
15 reaction mixture was filtered through Celite and the filtrate concentrated *in vacuo* to afford 0.29 g of an oil. To a solution of this oil in 1,4-dioxane was added NaHCO₃ (0.5M, 2.4 mLs). The resulting solution was concentrated *in vacuo* from toluene to afford **664** as
20 a waxy solid.

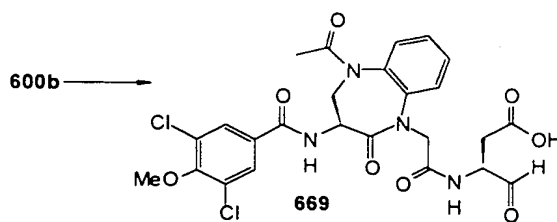
2-(Triisopropylsilyloxy)acetyl chloride (665), was synthesized from **664** by a method similar that used to prepare **643** to afford **665** as a crude product.

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyrac acid tert-butyl ester semicarbazone (666), was synthesized from **600b**, using **665**, by methods used to prepare **604d** from **600b** to afford 131 mg of **666**.
25

- 694 -

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(2-hydroxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyrac acid *tert*-butyl ester semicarbazone (**667**). To a solution of **666** (131 mg, 0.17 mmol) in tetrahydrofuran, cooled via ice-water bath, was added tetrabutylammonium fluoride (1M, 0.190 mL). After 2 hours the reaction mixture was poured into water, extracted twice with EtOAc, dried over MgSO₄ and concentrated *in vacuo* to afford 63 mg of **667** as a white solid.

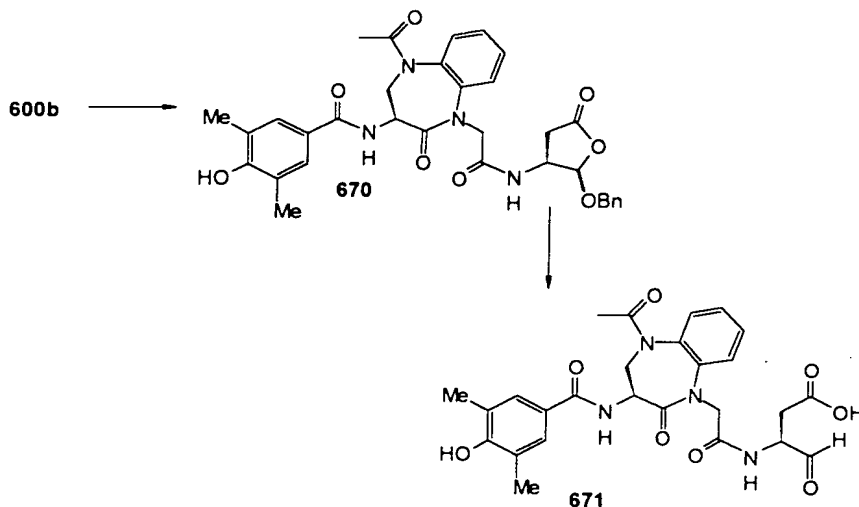
(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(2-hydroxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyrac acid (**668**), was synthesized from **667** by the methods used to prepare **605d** from **604d** to afford 48 mg of **668** as a white solid, ¹H NMR (CD₃OD) δ 2.45(m, 1H), 2.67(dddd, 1H), 3.78(d, 1H), 3.85(br. m, 1H), 4.05(d, 1H), 4.28(m, 1H), 4.5(m, 2H), 4.65(m, 1H), 4.95(br. s, 2H), 7.4-7.5(m, 4H), 7.52-7.65(m, 3H), 7.88(d, 2H).



(3S)-3-[(3S)-2-Oxo-3-(3,5-dichloro-4-methoxybenzoyl)amino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyrac acid (**669**), was synthesized from **600b** by the methods used to prepare **605d** from **600b** to afford 63 mg of **669** as a

- 695 -

white solid, ^1H NMR (CD_3OD) δ 1.9(s, 3H), 2.4-2.7(m, 2H), 3.6-3.7(m, 2H), 3.9(s, 3H), 4.2-4.4(m, 2H), 4.4-4.6(m, 3H), 7.4-7.8(m, 4H), 7.9(s, 2H).

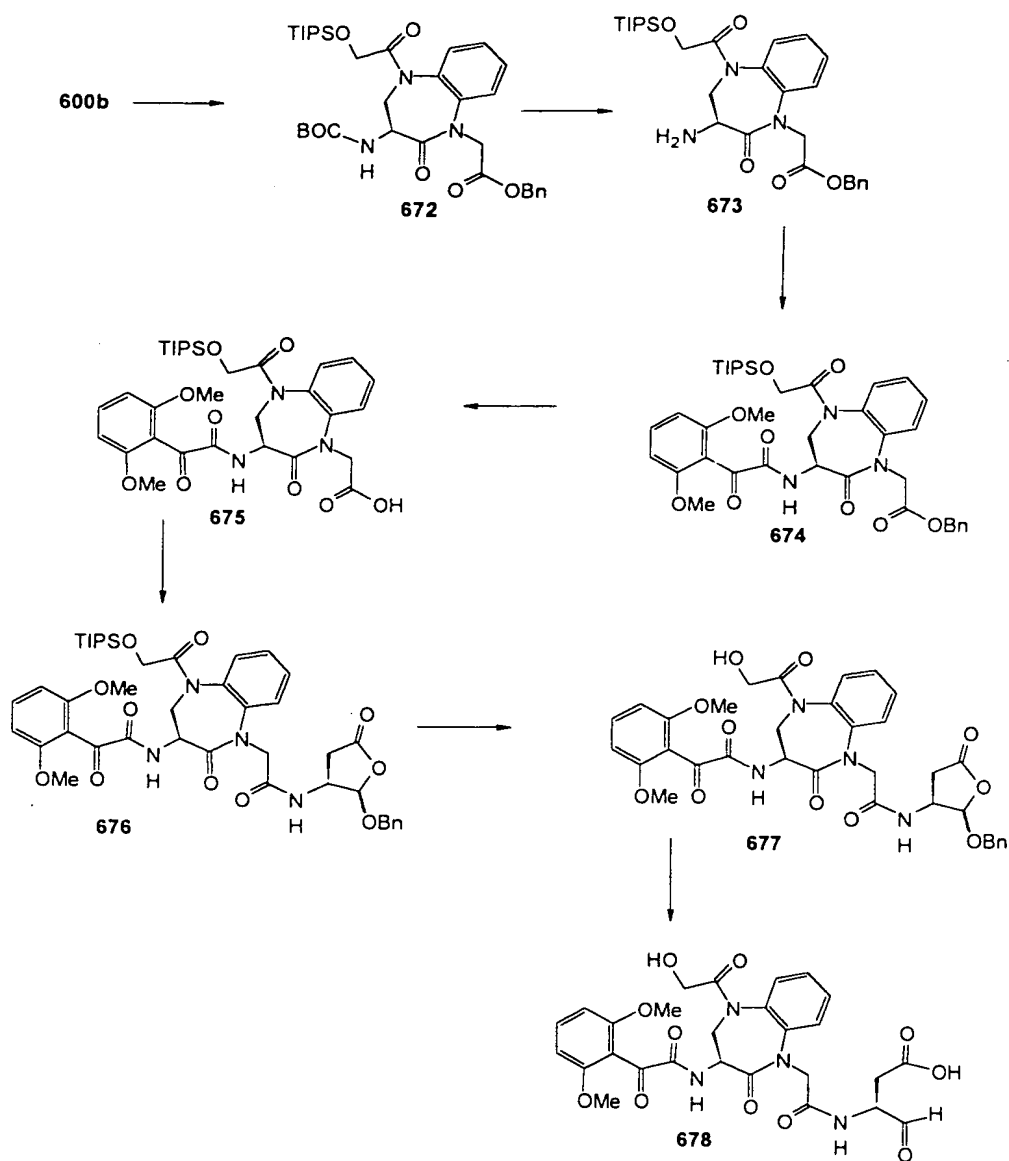


(3*S*)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-acetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetamide (670), was synthesized from 600b by the methods used to prepare 655 from 600b to afford 218 mg of 670 as a white solid, ^1H NMR (CD_3OD) δ 1.7, 1.75(2s, 3H), 2.15, 2.2(2s, 6H), 2.4-2.5(m, 1H), 2.6-2.75(m, 1H), 3.65-3.75(m, 2H), 4.2-4.3(m, 2H), 4.45-4.6(m, 3H), 7.35-7.6(m, 4H), 7.5(s, 2H).

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyrac acid (671), was synthesized from 670 by the methods used to prepare 2002 from 2001 to afford 253 mg of 671 as a white solid, ^1H NMR (CD_3OD) δ 1.9(s, 3H), 2.25(s, 6H),

- 696 -

2.4-2.5 (m, 1H), 2.6-2.75 (m, 1H), 3.65-3.75 (m, 2H), 4.2-4.3 (m, 2H), 4.45-4.6 (m, 3H), 7.35-7.6 (m, 4H), 7.5 (s, 2H).



- 697 -

(3S)-2-Oxo-3-*tert*-butoxycarbonylamino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzylester (672), was synthesized from 600b by method 1 used to prepare 602n
5 from 600b using 665 to afford 1.08 g of 672.

(3S)-2-Oxo-3-amino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzylester (673). To a solution of 672 (1.08 g, 1.69 mmol) in CH₂Cl₂ was added 2,6-lutidine (0.8 mL) then
10 TMSOTf (1 mL, 5.1 mmol). After 1 hour, the reaction mixture was poured into NaHCO₃ and extracted with CH₂Cl₂, dried over MgSO₄ and concentrated *in vacuo* to a small volume that was used directly for the next reaction.

15 (3S)-2-Oxo-3-(1,6-dimethoxybenzoyl formyl)amino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzylester (674), was synthesized from 673 by the method used to prepare 602b to afford 0.91 g of 674.

20 (3S)-2-Oxo-3-(1,6-dimethoxybenzoyl formyl)amino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid (675). A solution of 674 (0.365 g, 0.5 mmol) in MeOH was stirred with 1N NaOH (1.2 mL, 1.2 mmol). After 16 hours the reaction
25 mixture was concentrated *in vacuo* then dissolved in water and washed twice with ether. The aqueous layer was acidified with 1N HCl and the product extracted with EtOAc, dried over MgSO₄ and concentrated *in vacuo* to afford 337 mg of 675 as a solid.

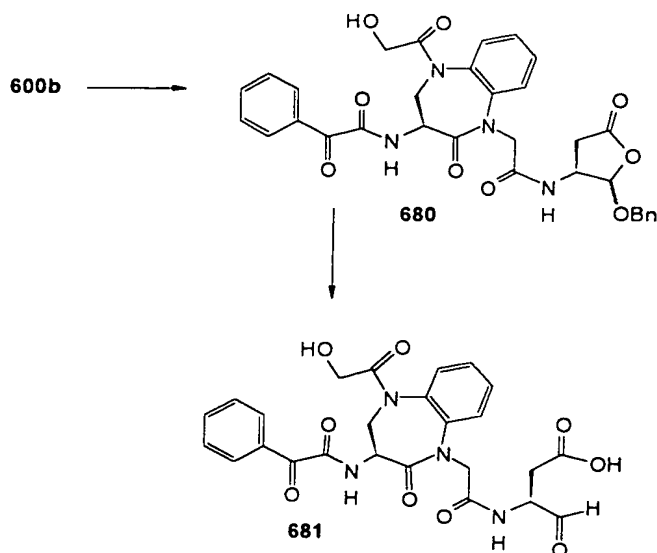
- 698 -

(3S)-2-Oxo-3-(1,6-dimethoxybenzoylformyl)amino-5-(2-triisopropylsilyloxy)acetyl-N-[(2RS,3S)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (676), was synthesized from
5 675 by the method used to prepare 213e to afford 166 mg of 676 as a white solid.

(3S)-2-Oxo-3-(1,6-dimethoxybenzoylformyl)amino-5-(2-hydroxy)acetyl-N-[(2RS,3S)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (677). A solution of TBAF
10 (6 mL, 3 mmol) in HOAc (0.46 mL, 8 mmol) was added to 676 (0.213 g, 0.256 mmol). After 16 hours the reaction mixture was poured into EtOAc and washed twice with NaHCO₃, once with brine then dried over MgSO₄ and
15 concentrated *in vacuo* to afford 139 mg of 677 as a solid, ¹H NMR (CDCl₃) δ 2.4(d, 1H), 2.5(dd, 1H), 2.8(dd, 1H), 2.92(dd, 1H), 3.15(m, 2H), 3.55-3.65(m, 2H), 3.72(s, 6H), 3.92(m, 1H), 4.05(m, 1H), 4.3(m, 1H), 4.42(d, 1H), 4.6(dd, 1H), 4.65-4.8(m, 2H), 4.88(d, 1H),
20 5.55(d, 1H), 6.55(m, 2H), 6.75(d, 1H), 7.25-7.55(m, 8H), 7.75(m, 2H).

(3S)-3-[(3S)-2-Oxo-3-(3,5-dimethoxybenzoylformyl)amino-5-(2-hydroxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyric acid (678),
25 was synthesized by the method used to prepare 667 from 666 to afford 54 mg of 678 as a white solid, ¹H NMR (CD₃OD) δ 2.45(m, 1H), 2.7(m, 1H), 3.5(m, 2H), 3.75(br. s, 6H), 4.05(d, 1H), 4.3(m, 1H), 4.51-4.6(m, 2H), 4.8(br. m, 2H), 6.7(d, 2H), 7.4-7.5(br. m, 3H), 7.6-
30 7.65(br. m, 2H).

- 699 -



(3*S*)-2-Oxo-3-benzoylformylamino-5-(2-hydroxy)acetyl-N-(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetamide (680), was synthesized from 600b by the methods used to prepare

5 677 from 600b to afford 140 mg of 680 as a white solid, ^1H NMR (CDCl_3) δ 2.31(d, 1H), 2.4(dd, 2H), 2.75(dd, 2H), 2.85(dd, 1H), 3.36(br. s, 1H), 3.45(br. s, 1H), 3.6(br. t, 2H), 3.82(br. m, 2H), 3.95(br. d, 2H), 4.35(m, 2H), 4.42(d, 1H), 4.55(m, 1H), 4.70(d, 1H), 4.82(br. s, 2H),

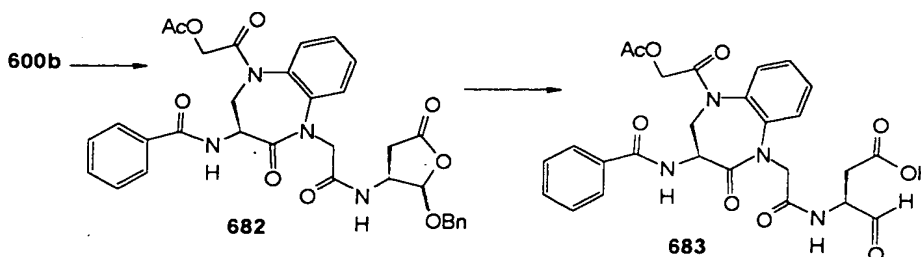
10 5.5(d, 1H), 6.91(d, 1H), 7.25(br. m, 5H), 7.35-7.46(br. m, 3H), 7.5-7.6(m, 2H), 8.15(br. d, 2H).

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylformylamino-5-(2-hydroxy)acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyrac acid (681),

15 was synthesized from 680 by the method used to prepare 678 from 677 to afford 45 mg of 681 as a grey solid, ^1H NMR (CD_3OD) δ 2.5(m, 1H), 2.7(dt, 1H), 3.65-3.85(br. m, 3H), 4.05(m, 1H), 4.3(m, 1H), 4.5-4.7(br. m, 3H),

- 700 -

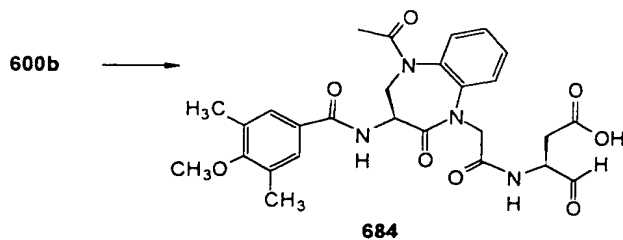
4.85(br. s, 2H), 7.3(br. m, 2H), 7.4-7.7(m, 5H),
8.15(d, 2H).



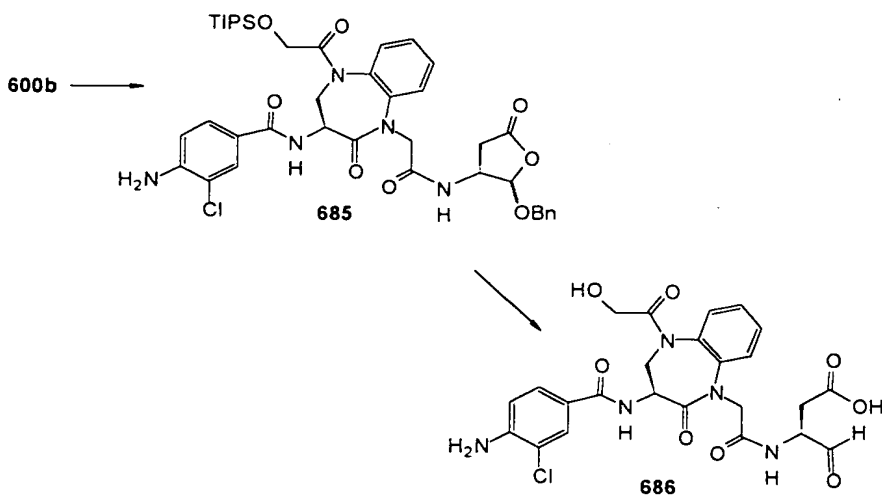
(3S)-2-Oxo-3-benzoylamino-5-(2-acetoxy)acetyl-N-
[(2RS,3S)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-
5 2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide
(682), was synthesized from 600b by the methods used to
prepare 655 from 600b to afford 495 mg of 682 as a
white solid, ^1H NMR (CDCl_3) δ 2.00(s, 3H), 2.05(s, 3H),
2.47(d, 1H), 2.58(dd, 1H), 2.85(dd, 1H), 2.89(dd, 1H),
10 3.9(m, 2H), 4.05-4.15(m, 2H), 4.19(dd, 1H), 4.45(m,
2H), 4.55-5.05(m, 8H), 5.55(d, 1H), 6.85(d, 1H),
7.15(d, 1H), 7.25-7.55(m, 10H), 7.75(d, 2H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(2-acetoxy)acetyl-
2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-
15 acetylamino]4-oxo-butyrac acid (683), was synthesized
from 682 by the method used to prepare 2002 from 2001
to afford 82 mg of 683 as a white solid, ^1H NMR (CD_3OD)
 δ 2.1(s, 3H), 2.5(m, 1H), 2.68(m, 1H), 3.8(m, 1H),
4.29(dd, 1H), 4.31(m, 1H), 4.45(d, 1H), 4.55(d, 1H),
20 4.6(d, 1H), 4.72(d, 1H), 4.95(br. s, 2H), 7.45(br. m,
2H), 7.52-7.65(br. m, 5H), 7.88(d, 2H).

- 701 -



(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethyl-4-methoxybenzoyl)amino-5-acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetyl]amino]4-oxo-butyrac acid (684), was synthesized from 600b by the method used to
 5 prepare 605d from 600b to afford 72 mg of 684 as a white solid, ^1H NMR (CD_3OD) δ 1.9(s, 3H), 2.25(s, 6H), 2.45(m, 1H), 2.6(m, 1H), 3.3(s, 1H), 3.7(s, 3H), 4.25(m, 1H), 4.45-4.6(m, 3H), 7.4(br. s, 2H), 7.55(br. d, 4H).

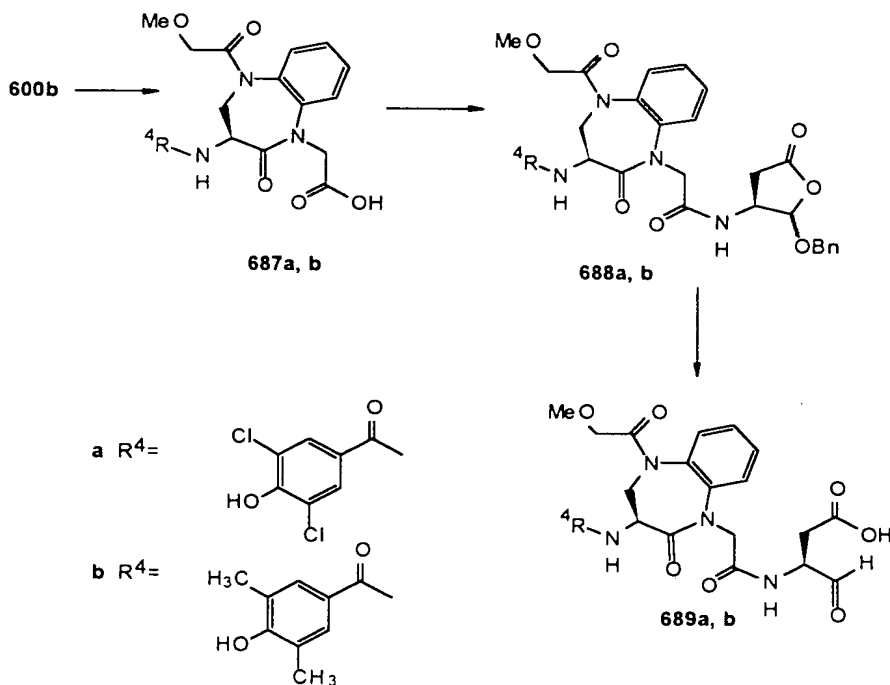


10 (3*S*)-2-Oxo-3-(3-chloro-4-aminobenzoyl)amino-5-(2-triisopropylsilyloxy)acetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1*H*-1,5-

- 702 -

benzodiazepine-1-acetamide (**685**), was synthesized from **600b** by the methods used to prepare **676** from **600b** to afford 165 mg of **685**.

(3*S*)-3-[(3*S*)-2-Oxo-3-(3-chloro-4-aminobenzoyl)amino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyric acid (**686**). To a solution of **685** (165 mg, 0.21 mmol) in THF was added a solution of TBAF (1*M*, 0.21 mL). The product was isolated by filtration after precipitation from reaction mixture. Reverse phase chromatography (10% to 80% MeCN in water/ 0.1% TFA) afforded 25 mg of **686** as a white solid, ^1H NMR (CD_3OD) δ 2.37-2.42 (m), 2.59-2.70 (m), 3.60-3.89 (m), 4.01 (d), 4.20-4.31 (m), 4.42-4.70 (m), 4.80-5.05 (m), 6.79 (d), 7.32-7.65 (m), 7.81 (s).



- 703 -

(3S)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid (**687a**), was synthesized from **600b** using methods similar to those used for preparing **654** from **600b** to afford 1.6 g of **687a**.

(3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid (**687b**), was synthesized from **600b** using methods similar to those used for preparing **654** from **600b** to afford 1.1 g of **687b**.

(3S)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-methoxyacetyl-N-[(2RS,3S)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (**688a**). To a solution of (3S,2R,S)-3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran (Chapman, Bioorg. Med. Chem. Lett., 2, pp. 613-618 (1992)) (1.13 g, 1.2 equiv) in CH₂Cl₂ was added triphenylphosphine (423 mg, 0.5 equiv), dimethylbarbituric acid (1.26 g, 2.5 equiv), and tetrakis(triphenylphosphine) palladium (0) (373 mg, 0.1 equiv). After 5 minutes the reaction mixture was cooled via ice-bath then added a solution of **687a** in DMF (1.6 g, 1 equiv), HOBT (480 mg, 1.1 equiv), and EDC (681 mg, 1.1 equiv). The resulting mixture was allowed to stir at ambient temperature. After 16 hours the reaction mixture was poured into NaHSO₄ and extracted twice with EtOAc. The organic layer was washed with NaHCO₃, brine, dried over Na₂SO₄ and concentrated in vacuo. Chromatography (SiO₂, 20% to 100% EtOAc in CH₂Cl₂) afforded 880mg of **688a** as an off-white solid, ¹H

- 704 -

NMR (CD₃OD) δ 2.55(dd, 1H), 2.7(dd, 1H), 3.0(m, 1H), 3.6(m, 1H), 3.75(d, 1H), 3.9-4.0(m, 2H), 4.3-4.45(m, 3H), 4.5-4.6(m, 3H), 4.7(m, 2H), 5.35(s, 1H), 5.55(d, 1H), 7.1-7.5(m, 4H), 7.85(s, 2H).

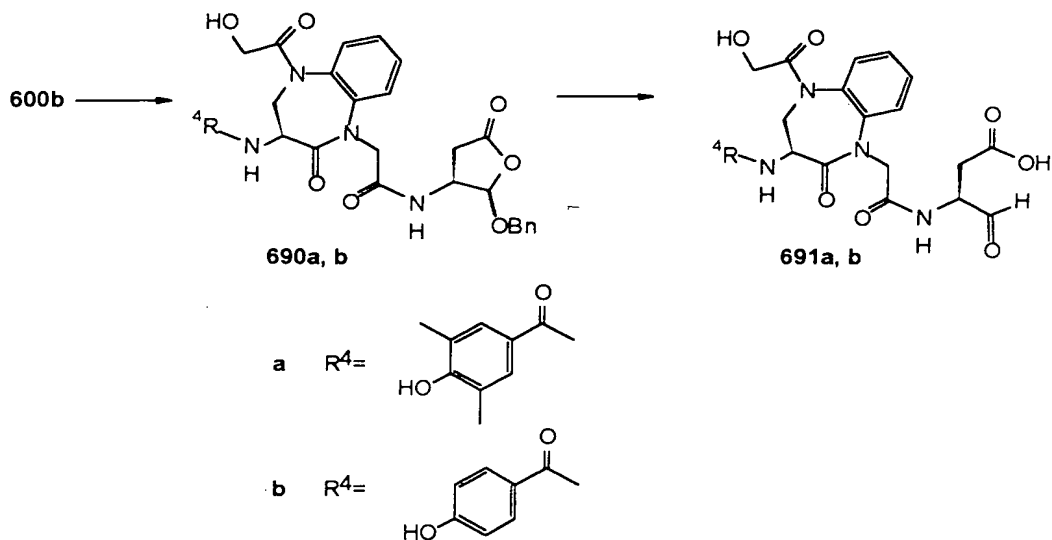
5 (3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-N-[(2RS,3S)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (688b), was synthesized from 687b by the method used to prepare 688a from 687a to
10 afford 960 mg of 688b as an off-white solid, ¹H NMR (CD₃OD) δ 2.6(dd, 1H), 2.7(dd, 1H), 3.0(dd, 1H), 3.2(s, 3H), 3.7(m, 3H), 3.9(m, 2H), 4.4-4.5(m, 2H), 4.6(m, 3H), 5.35(s, 1H), 5.55(d, 1H), 7.25(m, 2H), 7.4-7.5(m, 4H).

15 (3S)-3-[(3S)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyr-ic acid (689a), was synthesized from 688a by the method used to prepare 2002 from 2001 to afford 184 mg
20 of 689a as a white solid, ¹H NMR (CD₃OD) δ 2.45(m, 1H), 2.6(m 1H), 3.3(s, 3H), 3.7-3.85(m, 2H), 4.0(d, 1H), 4.3(m, 1H), 4.5-4.6(m, 3H), 7.3-7.6(m, 4H), 7.85(s, 2H).

(3S)-3-[(3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butyr-ic acid (689b), was synthesized from 688b by the method used to prepare 2002 from 2001 to afford 412 mg
25 of 689b as a white solid, ¹H NMR (CD₃OD) δ 2.5(m, 1H),

- 705 -

2.7(m, 1H), 3.3(s, 3H), 3.7-3.85(m, 2H), 4.05(dd, 1H),
4.3(m, 1H), 4.6(m, 2H), 7.45-7.4(m, 2H), 7.5(s, 2H),
7.55(m, 2H).



(3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-
5 hydroxyacetyl-N-[(2RS,3S)-benzyloxy-5-oxo-
tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-
benzodiazepine-1-acetamide (690a), was synthesized from
600b via methods used to prepare 676 from 600b, 688a
from 687a, then 677 from 676 to afford 863 mg of 690a
10 as a white solid, 1H NMR (CD_3OD) δ 2.2(s, 6H), 2.45(d,
0.5H), 2.6-2.9(m, 1H), 3.05(dd, 0.5H), 3.65-3.85(m,
2H), 3.95-4.1(m, 1H), 4.35-5.0(m, 7H), 5.35(s, 0.5H),
5.65(d, 0.5H), 7.2-7.4(m, 4H), 7.4-7.7(m, 7H).

(3S)-2-Oxo-3-(4-hydroxybenzoyl)amino-5-hydroxyacetyl-N-
15 [(2RS,3S)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-
2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide
(690b), was synthesized from 600b via methods used to
prepare 677 from 600b to afford 200 mg of 690b, 1H NMR

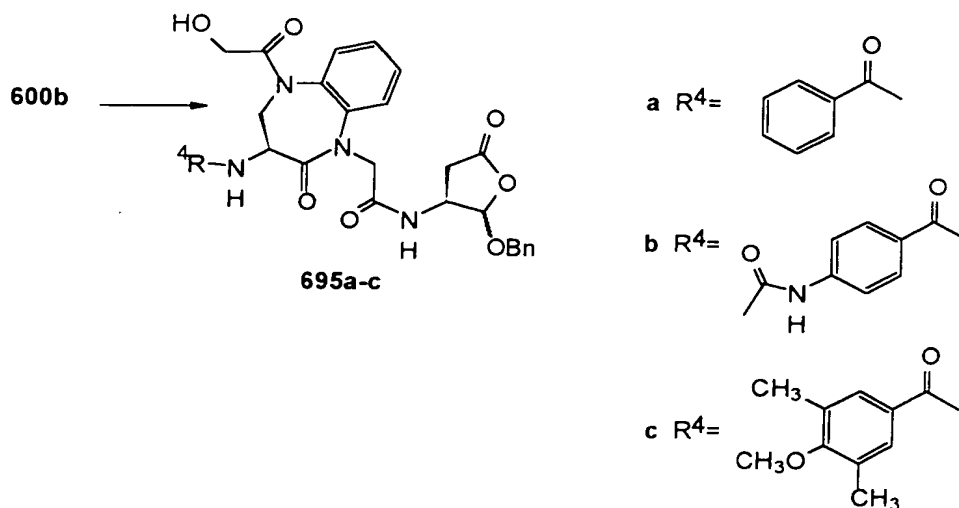
- 706 -

(CD₃OD) δ 2.49(d, 1H), 2.65(d, 1H), 2.66(d, 1H), 2.85(d, 1H), 2.87(d, 1H), 3.05(dd, 1H), 3.35(br. s, 1H), 3.72(br. s, 2H), 4.01(m, 2H), 4.45(br. m, 1H), 4.6(m, 1H), 4.7(m, 1H), 4.8(m, 1H), 4.95(br. s, 2H), 5.65(d, 1H), 6.8(d, 2H), 7.2-7.35(br. m, 3H), 7.45(m, 2H), 7.75(d, 2H).

(3S)-3-[(3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyr
10 **ic acid (691a)**, was synthesized from **690a** by the method used to prepare **2002** from **2001** to afford 560 mg of **691a** as a white solid, ¹H NMR (CD₃OD) δ 2.15(s, 6H), 2.45(m, 1H), 2.65(m, 1H), 3.55(m, 1H), 3.7(d, 1H), 4.0(d, 1H), 4.25(m, 1H), 4.5-4.6(m, 3H), 7.3-7.5(m, 6H).
15

(3S)-3-[(3S)-2-Oxo-3-(4-hydroxybenzoyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyr
20 **ic acid (691b)**, was synthesized from **690b** by the method used to prepare **2002** from **2001** to afford 410 mg of **691b** as a white solid, ¹H NMR (CD₃OD) δ 2.5(m, 1H), 2.65(m, 1H), 3.75(m, 1H), 3.8(d, 1H), 4.05(d, 1H), 4.25(m, 1H), 4.5(m, 1H), 4.6(m, 1H), 4.95(br. s, 2H), 6.8(d, 2H), 7.45(m, 2H), 7.6(m, 2H), 7.75(d, 2H).

- 707 -



(3*S*)-2-Oxo-3-benzoylamino-5-hydroxyacetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetamide (695a), was synthesized from 600b via methods used to prepare

5 677 from 600b to afford 75 mg of 695a, ¹H NMR (CD₃OD) δ 2.2(s, 6H), 2.45(m, 1H), 2.6(m, 1H), 3.65(m, 1H), 3.75(d, 1H), 4.0(d, 1H), 4.28(m, 1H), 4.5(m, 3H), 7.4-7.6(m, 6H).

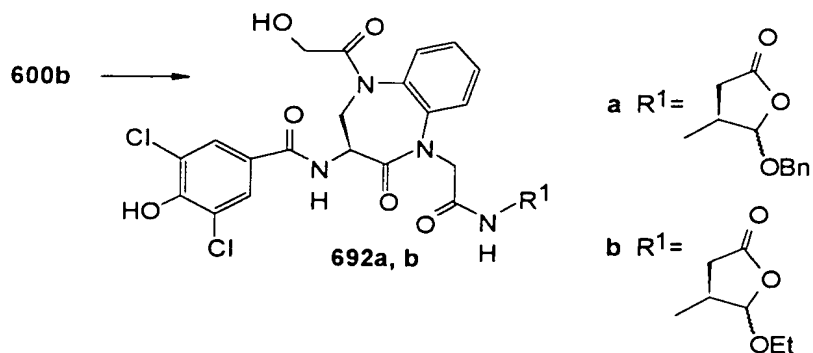
(3*S*)-2-Oxo-3-(4-acetamidobenzoyl)amino-5-hydroxyacetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetamide (695b), was synthesized from 600b via methods used to prepare 677 from 600b to afford 880 mg of 695b, ¹H NMR (CDCl₃) δ 2.1(s, 3H), 2.25-2.5(m, 2H), 2.8-2.92(m, 0.5H), 3.15-3.2(m, 0.5H), 3.45-3.6(m, 2H), 3.75-3.95(m, 2H), 4.15-4.25(m, 1H), 4.35-4.6(m, 2H), 4.6-4.88(m, 3H), 5.22(s, 0.25H), 5.33(s, 0.25H), 5.52-5.58(d, 0.5H), 7.15-7.45(m, 9.5H), 7.5-7.75(m, 5H), 8.3-8.35(m, 0.5H), 9.08-9.18(m, 1H).

10

15

- 708 -

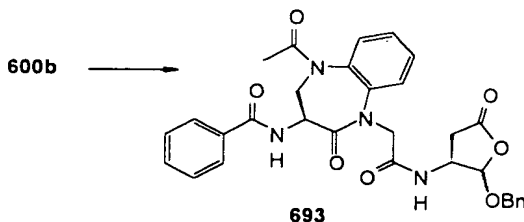
(3*S*)-2*RS*-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-hydroxyacetyl-N-(2-benzyloxy-5-oxo-tetrahydrofuran-3-yl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetamide (**695c**), was synthesized from **600b** via methods used to prepare **677** from **600b** to afford 840 mg of **695c**,
¹H NMR(CDCl₃) δ 2.23(s, 3H), 2.26(s, 3H), 2.45-2.62(m, 1H), 2.8-2.9(dd, 0.5H), 2.9-3.05(dd, 0.5H), 3.45-3.63(m, 1H), 3.64(s, 1.5H), 3.68(s, 1.5H), 3.78-4.05(m, 2H), 4.2-4.33(m, 1H), 4.4-4.63(m, 2H), 4.65-4.94(m, 2H), 4.95-5.1(m, 1H), 5.45(s, 0.5H), 5.5-5.6(d, 0.5H), 6.9-6.95(d, 1H), 7.25-7.7(m, 12H).



(3*S*)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-hydroxyacetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetamide (**692a**), was synthesized from **600b** via methods used to prepare **661** from **600b**, excluding steps used to make **604d** from **603d**, using instead the method to prepare **688a** from **687a** to afford 854 mg of **692a**,
¹H NMR (CD₃OD) δ 2.45(d, 1H), 2.6(m, 1H), 2.7(m, 1H), 3.0(m, 1H), 3.5-3.7(m, 4H), 4.0(q, 2H), 4.45(m, 3H), 4.55(m, 4H), 5.35(s, 1H), 5.6(d, 1H), 7.2-7.5(m, 9H), 7.85(s, 2H).

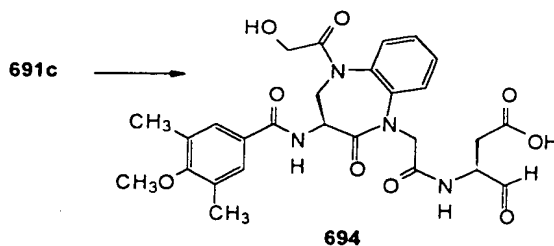
- 709 -

(3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-hydroxyacetyl-N-[(2RS,3S)-ethoxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (692b), was synthesized from 600b via methods used to prepare 661 from 600b, excluding steps used to make 604d from 603d, using instead the method to prepare 688a from 687a to afford 207 mg of 692b, ¹H NMR (CD₃OD) δ 1.05(t, 3H), 1.15(t, 3H), 2.45(d, 1H), 2.55(m, 1H), 2.7(m, 1H), 3.55(m, 2H), 3.6-3.75(m, 5H), 4.0(dd, 2H), 4.3(d, 1H), 4.4-4.7(m, 5H), 5.25(s, 1H), 5.5(d, 1H), 7.25-7.6(m, 4H), 7.85(s, 2H).



(3S)-2-Oxo-3-benzoylamino-5-acetyl-N-[(2RS,3S)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (693), was synthesized from 600b via methods used to prepare 688a from 600b to afford 30 mg of 693, ¹H NMR (CD₃OD) δ 1.7(s, 3H), 1.8(s, 3H), 2.51(d, 1H), 2.6(m, 1H), 2.85(m, 1H), 3.0(m, 1H), 3.75(br. d, 2H), 4.0-4.1(dd, 2H), 4.5-5.0(m, 6H), 5.45(s, 1H), 5.55(s, 1H), 7.15-7.85(m, 14H).

- 710 -

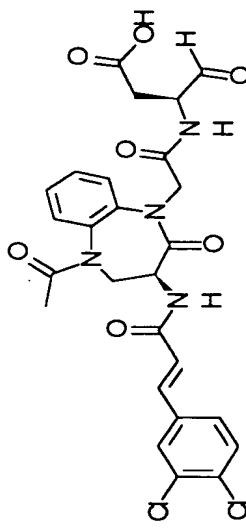
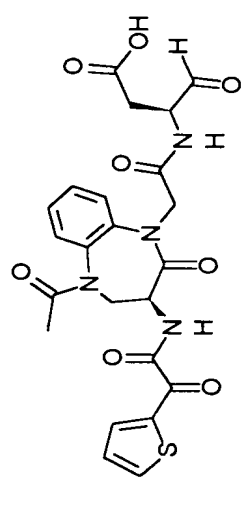


(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethyl-4-methoxybenzoyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetylamino]4-oxobutyrlic acid (**694**), was synthesized from **691c** by the method used to prepare **2002** from **2001** to afford 380 mg of **694** as a white solid, ^1H NMR (CD_3OD) δ 2.25(s, 6H), 2.45(m, 1H), 2.65(m, 1H), 3.65(m, 5H), 4.0(d, 1H), 4.28(m, 1H), 4.55(d, 2H), 4.95(m, 1H), 7.4-7.6(m, 6H).

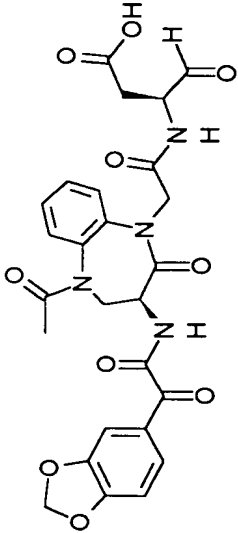
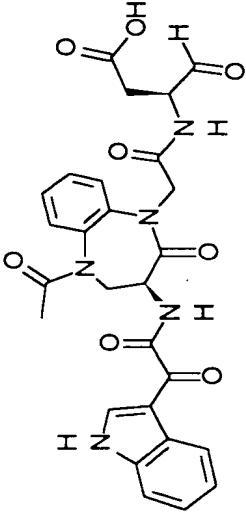
Compounds **700-711** were prepared by methods similar to the methods used to prepare compounds **619-635** (see, Example 13). Physical data for compounds **700-711** is listed in Table 25.

Compounds **910-915** and **918-921** were prepared as described below. Physical data for these compounds is listed in Table 26.

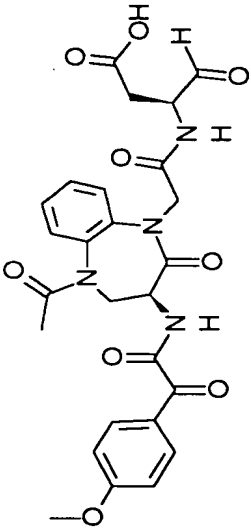
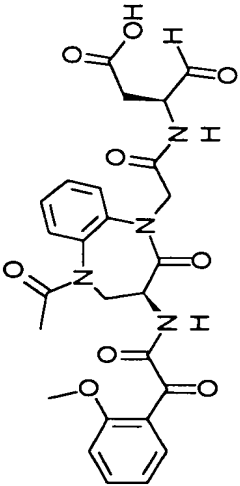
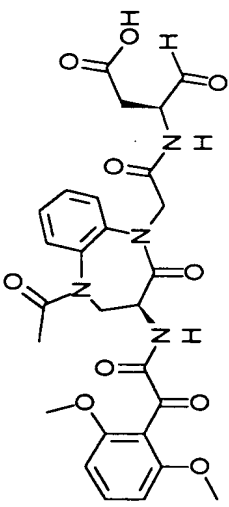
Table 25

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na) +
700		C26H24Cl2N4O7	575.41	14.061 (2) 97%	600
701		C23H22N4O8S	514.52	15.589 (1) 97%	538.8

- 712 -

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
702		C26H24N4O10	552.50	15.855 (1) 98%	575.9
703		C27H25N5O8	547.53	10.315 (2) 97%	572.1

- 713 -

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na) +
704		C26H26N4O9	538.52	10.475 (2) 96%	562.1
705		C26H26N4O9	538.52	14.260 (1) 72%	562.1
706		C27H28N4O10	568.55	14.836 (1) 97%	592.4

- 715 -

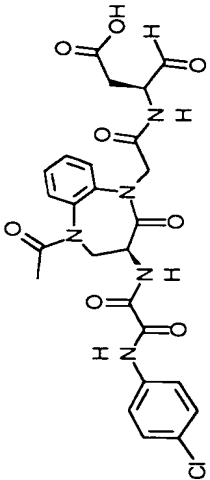
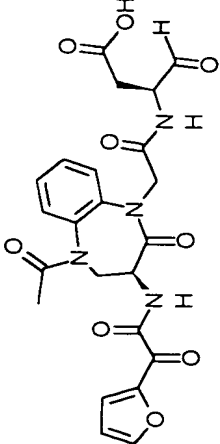
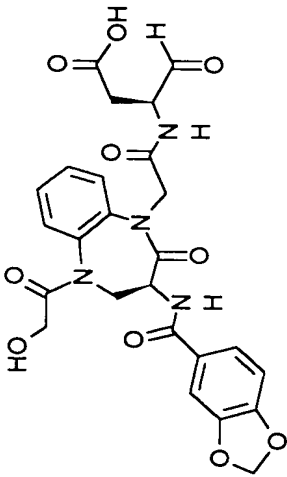
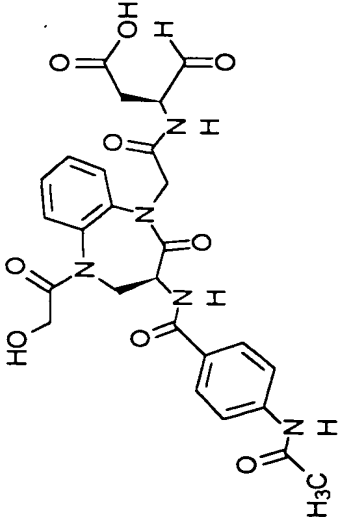
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na) +
710		C25H24ClN5O8	557.95	12.406 (2) 98%	582.2
711		C23H22N4O9	498.45	13.072 (1) 99%	521.9

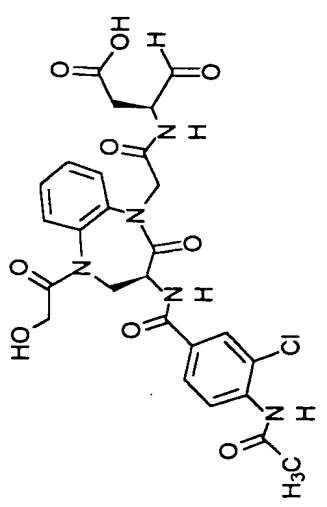
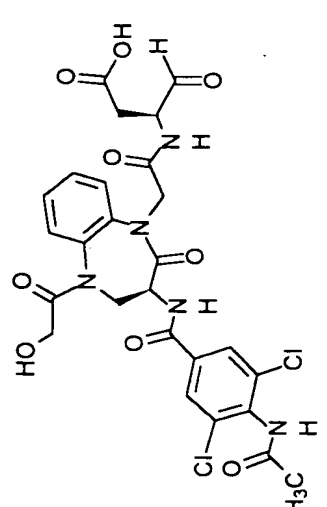
Table 26

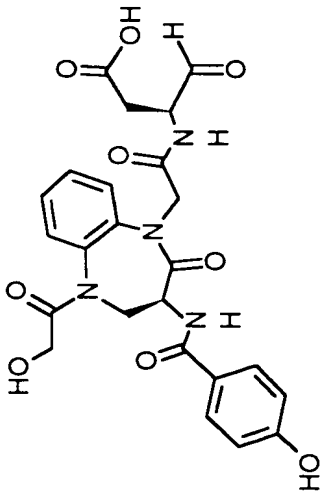
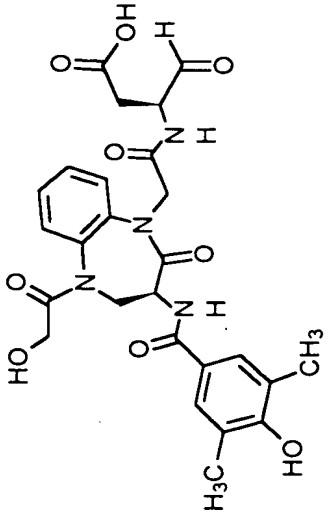
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na) +
910		C25H24N4O10	540.49	8.172 (2) 99%	564.4
911		C26H27N5O9	553.53	6.949 (2) 99%	577.5

- 717 -

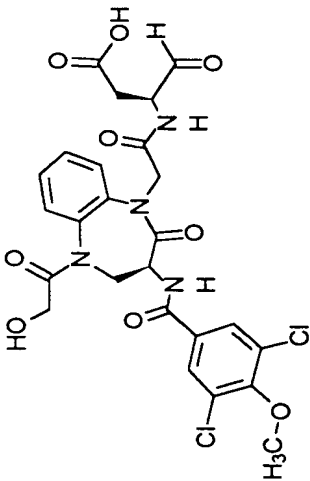
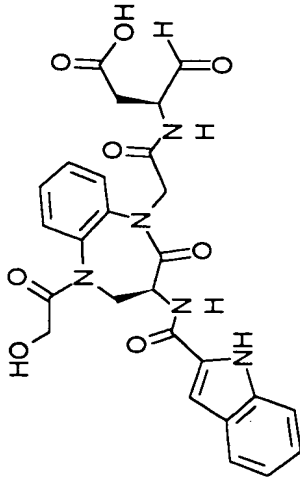
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na) +
912		C25H26N4O9	526.51	8.317 (2) 99%	550.7
913		C26H29N5O8	539.55	6.588 (2) 99%	563.5

- 718 -

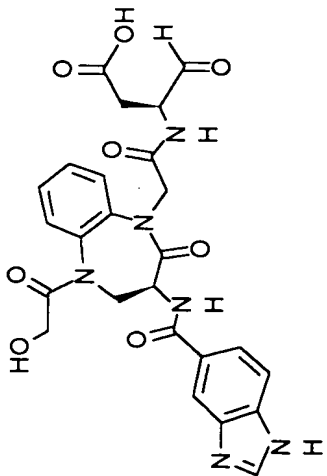
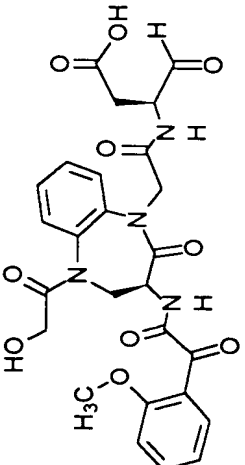
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na) +
914		C26H26ClN5O9	587.98	7.815 (2) 99%	612.2
915		C26H25Cl12N5O9	622.42	7.490 (2) 98%	647

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na) +
916/691b		C24H24N4O9	512.48	6.331 (2) 98%	537
917/691a		C26H28N4O9	540.53	8.114 (2) 99%	564.9

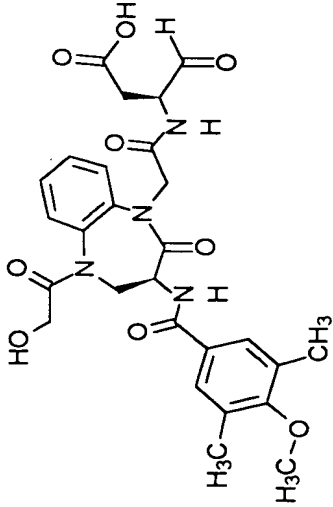
- 720 -

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na) +
918		C25H24Cl2N4O9	595.40	11.817 (2) 99%	619.3
919		C26H25N5O8	535.52	9.709 (2) 91%	559.7

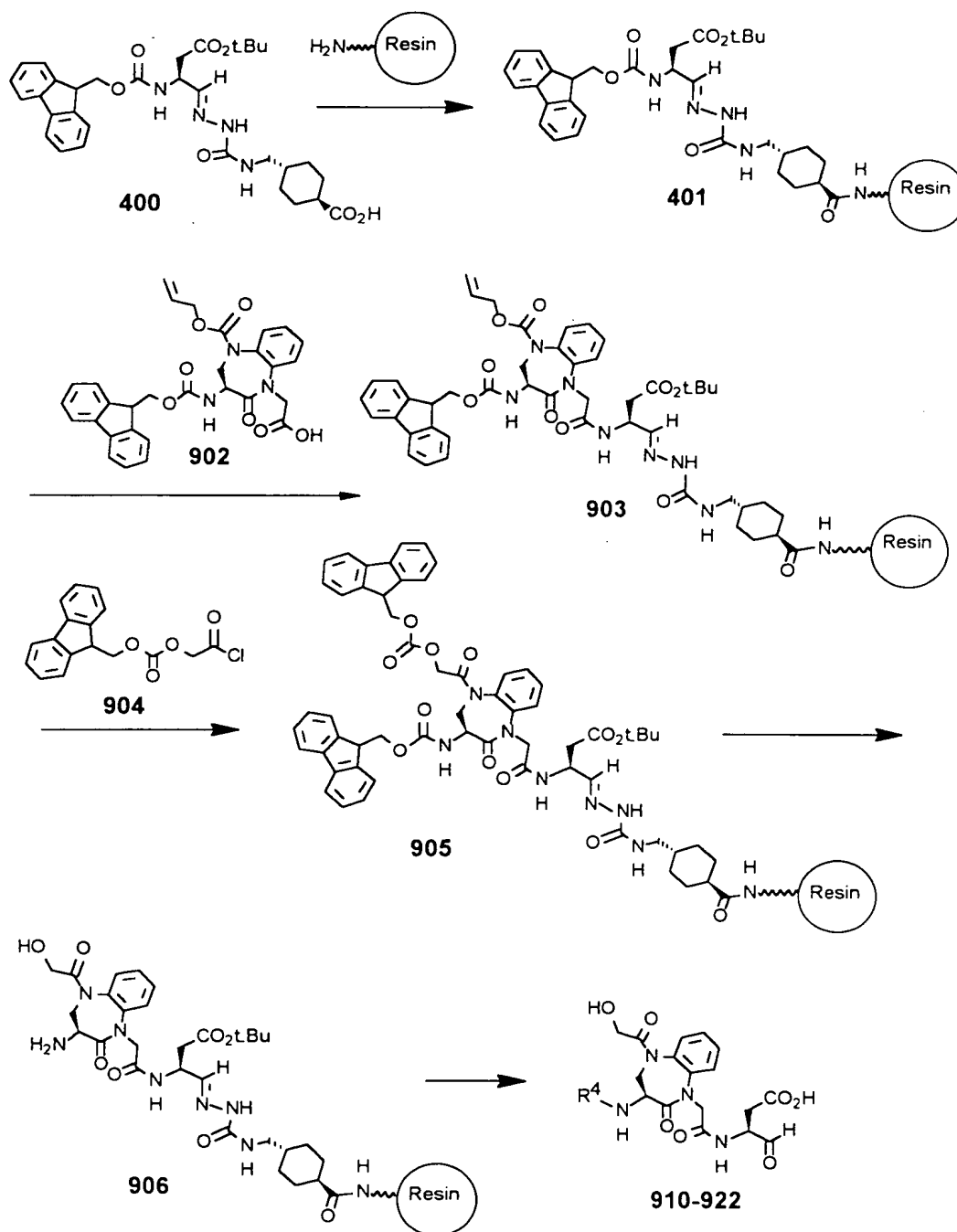
- 721 -

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na) +
920		C25H24N6O8	536.51	5.494 (2) 98%	560.6
921		C26H26N4O10	554.52	7.827 (2) 96%	579.1

- 722 -

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na) +
922/694		C27H30N4O9	554.56	10.024 (2) 99%	578.8

- 723 -



- 724 -

Step A. Synthesis of 401. TentaGel S® NH₂ resin (0.25 mmol/g, 6.8 g) was placed in a glass shaker vessel and washed with dimethylacetamide (3 X 20 mL). To a solution of **400** (1.70 g, 2.9 mmol, prepared from
5 (3S) 3-(fluorenylmethyloxycarbonyl)-4-oxobutryic acid t-butyl ester according to A.M. Murphy et. al. J. Am. Chem. Soc., 114, 3156-3157 (1992)) in dimethylacetamide (15 mL) was added O-benzotriazole-N,N,N,N'-tetramethyluronium hexafluorophosphate (HBTU; 1.09 g,
10 2.9 mmol), and DIEA (1.0 mL, 5.7 mmol). The solution was added to the resin, followed by dimethylacetamide (5 mL). The reaction mixture was agitated for 3 h at room temperature using a wrist arm shaker. The resin was isolated by suction filtration and washed with
15 dimethylacetamide (6 X 20 mL). A sample of resin (7.4 mg) was thoroughly washed with 50% methanol in dichloromethane and dried under suction. Deprotection of the Fmoc group using 20% piperidine in dimethylacetamide (10.0 mL) and UV analysis of the
20 solution revealed a substitution of 0.19 mmol g⁻¹.

Step B. Synthesis of 903. Resin **401** was deprotected with 20% (v/v) piperidine/dimethylacetamide (20 mL) for 10 min (shaking) and then for 10 min with
25 fresh piperidine reagent (20 ml). The resin was then washed with dimethylacetamide (6 X 20 ml). A solution of **902** (1.52 g, 2.81 mmol) was treated with HBTU (1.07 g, 2.83 mmol) and DIEA (1.0 mL, 5.7 mmol) and transferred to the resin, followed by dimethylacetamide
30 (5 mL). The reaction mixture was agitated for 2.5 h at room temperature using a wrist arm shaker. The resin was isolated by suction filtration and washed with

- 725 -

dimethylacetamide (4 X 20 mL) and dichloromethane (4 X 20 mL), and dried under nitrogen purge. Resin substitution was performed as described for **401** and determined to be 0.169 mmol g⁻¹.

5

Step C. Synthesis of 905. Resin **903** (7.54 g, 1.27 mmol) and dimedone (2.19 g, 15.6 mmol) were placed in a 100 mL round bottomed flask and freshly distilled anhydrous tetrahydrofuran (60 mL) was added.

10 Tetrakis(triphenylphosphine)palladium (0) (0.32 g, 0.28 mmol) was added and the nitrogen blanketed, sealed reaction was agitated for 15 h on a wrist action shaker. The resin was filtered, washed with dimethylacetamide (4 X 20 mL), dichloromethane (4 X 20

15 mL) and dimethylacetamide (1 X 20 mL). Sufficient dimethylacetamide was added to the resin to obtain a slurry followed by pyridine (1.5 mL, 18.5 mmol) and a solution of **904** (5.5 mmol) in dichloromethane (10 mL). The reaction was shaken under nitrogen for 8 h, then

20 filtered. The resin was washed with dimethylacetamide (5 X 20 mL) and dichloromethane (5 X 20 mL).

Step D. Synthesis of 906. This compound was prepared from resin **905** (0.24 g, 0.038 mmol) using an

25 Advanced ChemTech 396 Multiple Peptide synthesizer. The automated cycles consisted of a resin wash with dimethylformamide (3 X 1 mL), deprotection with 25% (v/v) piperidine in dimethylformamide (1 mL) for 10 min followed by fresh reagent (1 mL) for 20 min to yield

30 resin **906**. The resin was washed with dimethylformamide (3 X 1 mL) and N-methylpyrrolidone (3 X 1 mL).

- 726 -

Step E. (910-922) Resin 906 was acylated with a solution of 0.4M carboxylic acid and 0.4M HOBT in N-methylpyrrolidone (0.5 mL), a solution of 0.4M HBTU in N-methylpyrrolidone (0.5 mL) and a solution of 1.6M DIEA in N-methylpyrrolidone (0.25 mL) and the reaction was shaken for 2 hr at room temperature. The resin was washed with N-methylpyrrolidone (1 X 1 mL), dimethylformamide (4 X 1 mL), 50% methanol in dichloromethane (5 X 1 mL) and dried in air. The aldehyde was cleaved from the resin and globally deprotected by treatment with 95% TFA/ 5% H₂O (v/v, 1.5 mL) for 30 min at room temperature. After washing the resin with cleavage reagent (2 X 1 mL), the combined filtrates were added to cold 1:1 ether:hexane (35 mL) and the resulting precipitate was isolated by centrifugation and decantation. The resulting pellet was dissolved in acetonitrile (0.5 mL) and H₂O (0.5 mL) and filtered through 0.45 micron microcentrifuge filters. The compound was purified by semi-preparative RP-HPLC with a Rainin Microsorb™ C18 column (5 μ, 21.4 X 250 mm) eluting with a linear acetonitrile gradient (10% - 50%) containing 0.1% TFA (v/v) over 30 min at 12 mL/min. Fractions containing the desired product were pooled and lyophilized to provide 910-922.

25

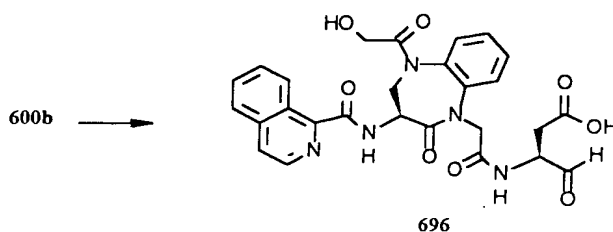
Analytical HPLC methods:

(1) Waters DeltaPak C18, 300Å (5μ, 3.9 X 150 mm). Linear acetonitrile gradient (0% - 25%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.

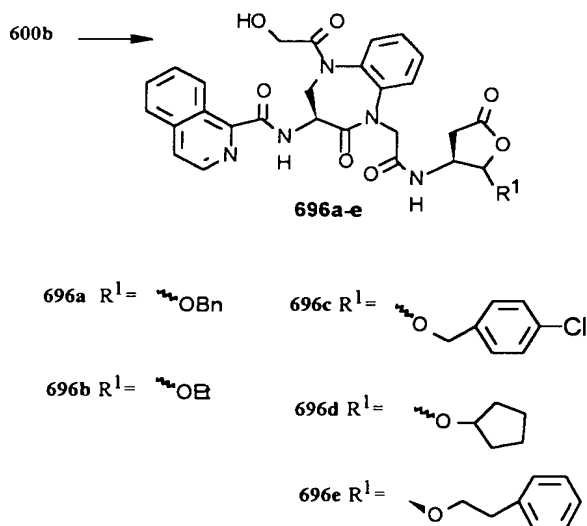
- 727 -

(2) Waters DeltaPak C18, 300Å (5μ, 3.9 X 150 mm).

Linear acetonitrile gradient (5% - 45%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.



(3*S*)-3-[(3*S*)-2-Oxo-3-(isoquinolin-1-yl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetyl-amino]4-oxo-butanoic acid (696) was synthesized from 600b by the method used to prepare 691a from 600b to afford 696. ¹H NMR (CD₃OD) δ 2.45(m, 1H), 2.7(m, 1H), 3.75(d, 1H), 3.95(q, 1H), 4.05(d, 1H), 4.3(m, 1H), 4.45-4.65(m, 2H), 5.05(m, 1H), 7.5-7.6(m, 3H), 7.7(t, 1H), 7.8(t, 1H), 7.98(t, 1H), 8.55(d, 1H), 9.1(d, 1H).



- 728 -

(3S)-2-Oxo-3-(isoquinolin-1-oyl)amino-5-hydroxyacetyl-N-[(2RS,3S)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (696a) was synthesized from 600b via methods used to
5 prepare 690a from 600b to afford 696a. ¹H NMR (CDCl₃) δ 0.95(t, 2H), 1.25(t, 1H), 1.4(m, 2H), 1.55(m, 1H), 2.55(m, 1H), 2.85(m, 1H), 2.95(dd, 1H), 3.15(m, 1H), 3.55(m, 1H), 3.9(m, 2H), 4.35(t, 1H), 4.4-4.55(m, 2H), 4.75(m, 1H), 4.8-5.05(m, 2H), 5.45(s, 1H), 5.55(d, 1H),
10 6.85(d, 1H), 7.15(d, 1H), 7.2-7.5(m, 5H), 7.6-7.8(m, 3H), 8.45(d, 1H), 9.05(d, 1H), 9.35(d, 1H).

(3S)-2-Oxo-3-(isoquinolin-1-oyl)amino-5-hydroxyacetyl-N-[(2RS,3S)-ethoxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-carboxamide (696b)
15 was synthesized from 600b via methods used to prepare 690a from 600b to afford 696b. ¹H NMR (CDCl₃) δ 0.9(m, 3H), 1.15(q, 3H), 1.15(m, 1H), 1.65(m, 1H), 2.5(m, 1H), 2.8(m, 1H), 2.95-3.0(m, 2H), 3.6(m, 2H), 3.7-3.85(m, 4H), 4.0(m, 2H), 4.3(m, 1H), 4.55(m, 1H), 4.65(m, 1H),
20 4.85-4.95(m, 1H), 5.05(m, 1H), 5.35(s, 1H), 5.45(d, 1H), 6.85(d, 1H), 7.25(d, 1H), 7.35-7.85(6H), 8.85(dd, 2H), 9.05(m, 1H), 9.35(dd, 2H).

(3S)-2-Oxo-3-(isoquinolin-1-oyl)amino-5-hydroxyacetyl-[2RS-(4-chlorobenzyl)oxy-5-oxo-tetrahydrofuran-3-yl]-
25 2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-carboxamide (696c) was synthesized from 600b via methods used to prepare 690a from 600b to afford 696c. ¹H NMR (CD₃OD) δ 1.25(t, 1H), 1.65(q, 1H), 1.9(m, 1H), 2.9(m, 1H),

- 729 -

3.05(m, 1H), 3.9(d, 1H), 4.2(m, 1H), 4.3(d, 1H), 4.7-5.0(m, 3H), 5.25(m, 1H), 5.7(s, 1H), 5.9(d, 1H), 7.5(d, 2H), 7.7-7.9(m, 3H), 8.0(t, 1H), 8.2(m, 2H), 8.75(d, 1H), 9.35(d, 1H).

5 **(3S)-2-Oxo-3-(isoquinolin-1-oyl)amino-5-hydroxyacetyl-(2RS-cyclopentyloxy-5-oxo-tetrahydrofuran-3-yl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-carboxamide (696d)** was synthesized from **600b** via methods used to prepare **690a** from **600b** to afford **696d**. ¹H NMR (CDCl₃) δ

10 0.9(t, 1H), 1.2(t, 1H), 1.3-1.45(m, 2H), 1.6-1.8(m, 4H), 2.45(m, 1H), 2.8(m, 1H), 3.0(m, 1H), 3.4(q, 1H), 3.5(d, 1H), 4.0(m, 2H), 4.2-4.3(m, 2H), 4.55(d, 1H), 4.65(m, 1H), 4.9(m, 1H), 5.05(m, 1H), 5.4(s, 1H), 5.5(d, 1H), 6.8(d, 1H), 7.3-7.9(m, 6H), 8.5(d, 1H),

15 9.05(d, 1H), 9.4(d, 1H).

(3S)-2-Oxo-3-(isoquinolin-1-oyl)amino-5-hydroxyacetyl-N-[(2R,3S)-phenethoxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (696e) was synthesized from **600b** via methods used to

20 prepare **690a** from **600b** to afford **696e**. ¹H NMR (CDCl₃) δ

1.2(t, 1H), 2.4(m, 1H), 2.8(m, 2H), 3.6(d, 1H), 3.7(q, 1H), 4.0(m, 2H), 4.3(d, 2H), 4.65(m, 1H), 4.85(t, 1H), 5.0(m, 1H), 5.35(d, 1H), 6.5(d, 1H), 7.15-7.85(m, 8H), 8.45(d, 1H), 9.05(d, 1H), 9.4(d, 1H).

- 730 -

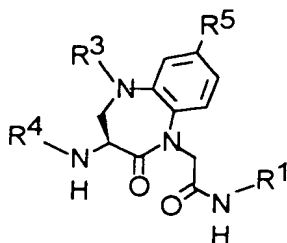
Example 32Table 27

	Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
	688c	200				
5	689b-1	3.5		2700		
	696-1	0.5				
	696-2	0.5				
	697	1.8		5000		
	698	18		13500		
10	699	1.1				
	699a-2					
	720	2.7				
	721	1.3		5000		
	722	5		5000		
15	723	2.3		2000		
	724	2		1800		
	725	3.7		3000		
	726	300				
	727	50		2300		
20	728	300				
	729	28		2800		
	730	90		8000		
	731	150				
	732	5		1800		
25	733	5		1500		
	734	9		6000		
	735	6		10000		

- 731 -

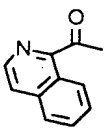
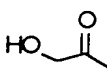
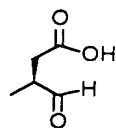
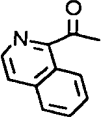
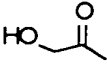
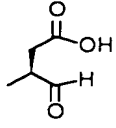
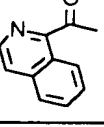
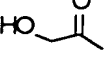
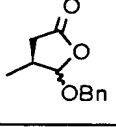
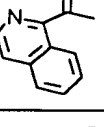
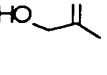
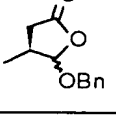
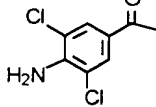
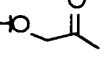
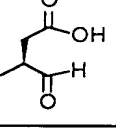
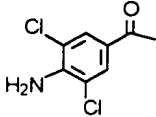
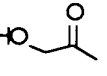
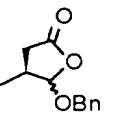
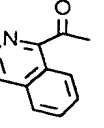

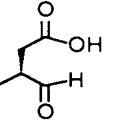
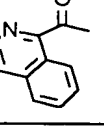

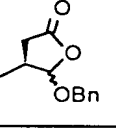
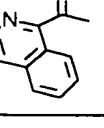
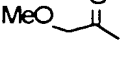
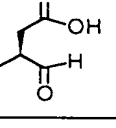
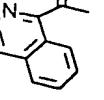
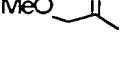
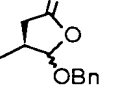
Example 33

Compounds 684a, 688b-1, 688c, 689b-1, 690a-1, 696-1, 696-2, 696a-2, 696a-1, 697, 697a, 698, 698a, 699, 699a, 699a-1, 699a-2, 800 and 801 were prepared as
5 described below.

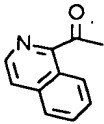
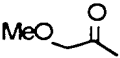
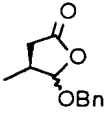
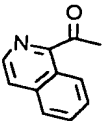
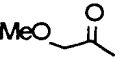
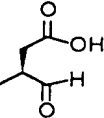
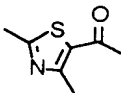
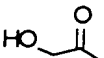
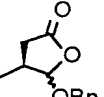
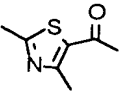
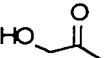
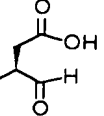
Table 28

CIP#	R ⁴	R ³	R ⁵	R ¹
684a			H	
688b-1			F	
688c			H	
689b-1			F	
690a-1			H	

- 732 -

CIP#	R ⁴	R ³	R ⁵	R ¹
696-1			F	
696-2			Cl	
696a-2			Cl	
696a-1			F	
697			H	
697a			H	
698			H	
698a			H	
699			H	
699a			H	

- 733 -

CIP#	R ⁴	R ³	R ⁵	R ¹
699a-1			F	
699a-2			F	
800			H	
801			H	

5 (3S)-3-[(3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl-amino]4,4-diethoxybutyric acid ethyl ester(690a-1), was synthesized by the methods used to prepare 690a and
 10 2100b to afford 690a-1, ¹H NMR(CDCl₃) δ 1.15(t, 6H), 1.3(t, 3H), 2.25(s, 6H), 2.60(d, 2H), 3.50(m, 2H), 3.70(m, 4H), 4.05(m, 2H), 4.15(m, 2H), 4.30(d, 1H), 4.45(m, 1H), 4.50(d, 1H), 4.55(d, 1H), 4.70(t, 1H), 5.05(m, 1H), 5.30(s, 1H), 6.70(d, 1H), 7.10(d, 2H),
 15 7.30-7.50(m, 7H)

(3S)-2-Oxo-3-(3,5-dichloro-4-aminobenzoyl)amino-5-hydroxyacetyl-N-[(2RS,3S) 2-benzyloxy-5-oxotetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide(697a) was synthesized via
 20 methods used to prepare 677 to afford 840 mg of 697a, ¹H NMR (CDCl₃) δ 1.78 (br. s, 2H), 2.48-2.58 (d, 0.5H),

- 734 -

2.6-2.7 (m, 0.5H), 2.8-2.9 (m, 0.5H), 2.92-3.03 (m, 0.5H), 3.55-3.8 (m, 2H), 3.92-4.02 (d, 1H), 4.25-4.3 (d, 0.5H), 4.37-4.42 (d, 0.5H), 4.43-4.48 (m, 0.5H), 4.55-4.65 (m, 1.5H) 4.7-5.12 (m, 5H), 5.44 (s, 0.5H),
 5 5.58-5.63 (d, 0.5H), 6.95-8.1 (m, 13H).

(3S)-3-[(3S)-2-Oxo-3-(3,5-dichloro4-aminobenzoyl)amino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxobutyric acid (697) was synthesized via methods used to prepare 2002 from 2001 to afford 140 mg
 10 of 697, ^1H NMR (CD_3OD) δ 2.38-2.5 (m, 1H), 2.55-2.75 (m, 1H), 3.68-3.9 (m, 3H), 3.95-4.03 (m, 1H), 4.2-4.3 (m, 1H), 4.4-4.7 (m, 4H), 7.35-7.8 (m, 6H).

(3S)-3-[(3S)-2-Oxo-3-(3,5-dimethyl-4-methoxybenzoyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetyl-amino]4-acetoxy-3-butenic acid ethyl ester (684a), was
 15 synthesized by the methods used to prepare 2100j to afford 684a, ^1H NMR (500 MHz, CDCl_3 mixture of diastereomers) δ 1.3 (s, 9H), 1.8 (s, 3H), 2.1 (s, 3H), 2.15 (s, 3H), 2.3 (s, 6H), 3.3-3.5 (m, 3H), 3.65 (s, 3H), 3.9 (m, 1H), 4.1 (d, 1H), 4.3 (d, 1H), 4.6-4.8 (m, 3H), 5.0 (m, 1H), 6.7 (s, 1H), 7.0 (d, 1H), 7.1 (d, 1H), 7.2-7.5 (m, 6H).

(3S)-2-Oxo-3-isoquinolin-1-yl-amino-5-formyl-N-[(2RS,3S) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (698a) was synthesized via methods used to
 25 prepare 652 to afford 795 mg of 698a ^1H NMR (500 MHz, CDCl_3 mixture of diastereomers) δ 2.8 (m, 2H), 4.0 (m, 1H), 4.5-4.8 (m, 4H), 5.2 (m, 1H), 5.5 (s, 1H), 5.75 (d,
 30

- 735 -

1H), 7.3-7.85(m, 11H), 7.9(t, 1H), 8.2(d, 1H), 8.6(m, 1H), 9.3(m, 1H).

(3S)-3-[(3S)-2-Oxo-3-isoquinolin-1-oylamino-5-formyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-

5 **acetylamino]4-oxobutyric acid(698)** was synthesized via methods used to prepare 653 to afford 225 mg of 698 ¹H NMR (500 MHz, CD₃OD) δ 2.4(m, 1H), 2.6(m, 1H), 3.9(m, 1H), 4.2(m, 1H), 4.3-4.7(m, 4H), 5.1(m, 1H), 7.3-7.5(m, 4H), 7.6-7.8(m, 2H), 7.8(m, 2H), 8.2(d, 1H), 8.5(d, 10 1H), 9.0(d, 1H).

(3S)-2-Oxo-3-isoquinolin-1-oylamino-5-methoxyacetyl-N-[(2RS,3S) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-

acetamide(699a) was synthesized via methods used to 15 prepare 655 to afford 820 mg of 699a as a tan solid, ¹H NMR (500 MHz, CDCl₃) δ 2.60 (ddd, 1H), 2.90 (ddd, 1H), 3.20 (s, 3H), 3.25 (s, 3H), 3.70 (t, 1H), 3.90 (m, 2H), 4.20 (dd, 1H), 4.60 (m, 2H), 4.70-5.00 (m, 5H), 5.55 (d, 1H), 7.00 (d, 1H), 7.20-7.50 (m, 7H), 8.45 (dd, 20 1H), 9.0 (dd, 1H), and 9.35 ppm (dd, 1H).

(3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-N-[(2RS,3S) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-benzodiazepine-1-acetamide(688b-1) was synthesized

25 via methods used to prepare 655 to afford 600 mg of 688b-1, ¹H NMR (CDCl₃; mix. of diastereomers) δ 2.21 (s, 3H), 2.28 (s, 3H), 2.42-2.50 (m, 0.5 H), 2.58-2.65 (m, 0.5H), 2.83-2.91 (m, 0.5H), 2.98-3.1 (m, 0.5H), 3.18 (s, 1.5H), 3.22 (s, 1.5H), 3.72-3.78 (d, 1H), 3.78-30 3.9 (m, 2H), 4.08-4.15 (d, 1H), 4.5-4.69 (m, 3H), 4.7-

- 736 -

4.85 (m, 1H), 4.88-5.1 (m, 2H), 5.45 (s, 0.5H), 5.55-5.65 (d, 0.5H), 6.85-6.92 (m, 1H), 7.02-7.13 (m, 2H), 7.24-7.55 (m, 9H).

5 (3S)-3-[(3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid(689b-1) was synthesized via methods used to prepare 2002 from 2001 to afford
10 689b-1, ¹H NMR (CD₃OD) δ 2.18 (s, 6H), 2.36-2.47 (m, 1H), 2.6-2.72 (m, 1H), 3.34 (s, 3H), 3.66-3.88 (m, 2H), 3.95-4.05 (m, 1H), 4.2-4.78 (m, 5H), 4.9 (m, 1H), 7.3-7.41 (m, 2H), 7.48 (s, 2H), 7.5-7.63 (m, 1H).

(3S)-3-[(3S)-2-Oxo-3-isoquinolin-1-oylamino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid(699) was synthesized via methods used to prepare 2002 from 2001 to afford
15 699 as a white solid, ¹H NMR (500 MHz, CD₃OD) δ 2.50 (m, 1H), 2.70 (m, 1H), 3.25 (s, 3H), 3.80 (bd, 1H),
20 3.90 (bd, 1H), 4.00 (bd, 1H), 4.30 (m, 1H), 4.50-4.70 (m, 3H), 4.80-4.85 (bt, 1H), 5.00 (bm, 1H), 7.40-7.55 (m, 5H), 7.70 (bm, 1H), 7.85 (bm, 1H), 8.00 (bm, 1H), 8.55 (bd, 1H), and 9.05 ppm (bd, 1H).

(3S)-2-Oxo-3-isoquinolin-1-oylamino-5-hydroxyacetyl-N-
25 [(2RS,3S) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-benzodiazepine-1-acetamide(696a-1) was synthesized via methods used to prepare 656 to afford 800 as a yellow solid, ¹H NMR (500 MHz, CDCl₃) δ 2.55 (ddd, 1H), 2.85 (ddd, 1H),
30 3.70-3.80 (m, 2H), 3.95 (bm, 1H), 4.05 (d, 1H), 4.30 (d, 1H), 4.40-4.60 (m, 4H), 4.70-5.05 (m, 4H), 5.55

- 737 -

(d, 1H), 7.10 (d, 1H), 7.20-7.35 (m, 3H), 7.40- 7.50 (m, 1H), 7.60- 7.85 (m, 3H), 8.40 (dd, 1H), 9.10 (m, 1H), and 9.30 pp (m, 1H).

(3S)-2-Oxo-3-isoquinolin-1-oylamino-5-hydroxyacetyl-N-
5 [(2RS,3S) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-
2,3,4,5-tetrahydro-7-chloro-1H-1,5-benzodiazepine-1-
acetamide (696a-2) was synthesized via methods used to
prepare 677, to afford 204 mg of 696a-2 as a white
solid, with the exception that the reduction of the
10 nitro- group was done as follows: To a solution of the
nitro compound (7.2 g, 20 mmol) in MeOH was added NH₄Cl
(2.1 g, 39 mmol) and Zn (17 g, 260 mmol). The
resulting mixture was heated to reflux 1 hour after
which it was cooled and filtered through celite. The
15 filtrate was concentrated in vacuo then treated with
cold 1N HCl to afford 3.6 g of a pale red solid. ¹H
NMR(CDCl₃) δ 1.85(s, 1H), 2.45(d, 0.5H), 2.50-2.65(m,
0.5H), 2.80-2.90(m, 0.5H), 2.90-3.00(m, 0.5H), 3.45(s,
0.5H), 3.55-3.75(m, 1H), 3.85-4.15(m, 2H), 4.25(d, 1H),
20 4.40-4.65(m, 2H), 4.70-4.80(m, 0.5H), 4.85-5.15(m, 3H),
5.40(s, 0.5H), 5.60(d, 0.5H), 7.00(d, 0.5H), 7.15-
7.90(m, 12.5H), 8.35-8.45(m, 1H), 9.00-9.10(m, 1H),
9.25-9.40(m, 1H)

(3S)-3-[(3S)-2-Oxo-3-isoquinolin-1-oylamino-5-
25 hydroxyacetyl-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-
benzodiazepine-1-acetyl-amino]4-oxobutyric acid(696-1)
was synthesized via methods used to prepare 2002 from
2001 to afford 140 mg of 696-1 as a white solid, ¹H NMR
(500 MHz, CD₃OD) δ 2.50 (m, 1H), 2.70 (m, 1H), 3.85 (d,
30 1H), 3.95 (m, 1H), 4.10 (d, 1H), 4.35 (m, 1H), 4.50-
4.60 (m, 2H), 4.80 (bm, 1H), 5.00 (m, 1H), 7.40- 7.48

- 738 -

(m, 3H), 7.65 (m, 1H), 7.75 (t, 1H), 7.85 (t, 1H), 8.00 (d, 1H), 8.55 (d, 1H), and 9.05 ppm (d, 1H).

(3S)-3-[(3S)-2-Oxo-3-isoquinolin-1-oylamino-5-hydroxyacetyl-2,3,4,5-tetrahydro-7-chloro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxobutyric acid(696-2)
5 was synthesized via methods used to prepare 2002 from 2001 to afford 250 mg of 696-2 as a white solid, ¹H NMR(CD₃OD) δ 2.40-2.55(m, 1H), 2.60-2.75(m, 1H), 3.80-4.00(m, 2H), 4.05(d, 1H), 4.20-4.35(m, 1H), 4.45-
10 4.65(m, 3H), 4.80-5.10(m, 2H)

(3S)-2-Oxo-3-isoquinolin-1-oylamino-5-methoxyacetyl-N-[(2RS,3S) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-benzodiazepine-1-acetamide(699a-1) was synthesized via methods used to
15 prepare 655 to afford 699a-1 ¹H NMR (500 MHz, CDCl₃) δ 2.55 (ddd, 1H), 2.90 (ddd, 1H), 3.25 (s, 3H), 3.28 (s, 3H), 3.80 (bt, 2H), 3.95 (bm, 2H), 4.25 (dd, 1H), 4.45-4.90 (m, 3H), 5.60 (d, 1H), 7.05- 7.40 (m, 8H), 7.50 (bm, 1H), 7.65- 7.85 (m, 2H), 8.45 (d, 1H), 9.1 (m,
20 1H), and 9.35 ppm (m, 1H)

(3S)-3-[(3S)-2-Oxo-3-isoquinolin-1-oylamino-5-methoxyacetyl-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-benzodiazepine-1-acetyl-amino]4-oxobutyric acid(699a-2) was synthesized via methods used to prepare 2002 from
25 2001 to afford 699a-2 ¹H NMR (500 MHz, CD₃OD) δ 2.51 (m, 1H), 2.70 (dt, 1H), 3.31 (bs, 3H), 3.90 (bdt, 1H), 3.95 (bm, 1H), 4.05 (d, 1H), 4.35 (m, 1H), 4.50 (d, 1H), 4.60 (dd, 1H), 4.65 (dt, 1H), 4.80 (m, 1H), 5.05 (m, 1H), 7.35- 7.48 (m, 3H), 7.65 (bm, 1H), 7.75 (t,

- 739 -

1H), 7.82 (t, 1H), 8.05 (d, 1H), 8.55 (d, 1H), and 9.05 ppm (d, 1H).

(3S)-3-[(3S)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid, O-2,6-dichlorobenzyl oxime(688c) was synthesized via methods used to prepare 308d to afford 800, ¹H NMR (CD₃OD) δ 2.2 (s, 6H), 2.58-2.83 (m, 2H), 3.28 (s, 3H), 3.29-3.34 (m, 1H), 3.68-3.80 (m, 2H), 3.95-4.05 (dd, 1H), 4.38-4.48 (dd, 1H), 4.82-5.00 (m, 2H), 5.26-5.36 (m, 2H), 7.22-7.65 (m, 10H).

(3S)-2-Oxo-(2,4-dimethylthiazo-5-yl)amino-5-hydroxyacetyl-N-[(2RS,3S) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide(800) was synthesized via methods used to prepare 696a-1 to afford 204 mg of 800 as a yellow solid, ¹H NMR(CDCl₃) (mixture of diastereomers) δ 1.70(s, 1H), 2.40-2.80(m, 7H), 2.80-2.90(m, 0.5H), 2.95-3.05(m, 0.5H), 3.30-3.35(m, 0.5H), 3.45-3.55(m, 0.5H), 3.55-3.65(m, 1H), 3.80-4.05(m, 2H), 4.30-4.50(m, 2H), 4.55-4.65(m, 1H), 4.75-4.95(m, 3H), 5.45(s, 0.5H), 5.55(d, 0.5H), 6.70(d, 0.5H), 6.90(d, 0.5H), 7.15-7.80(m, 10H)

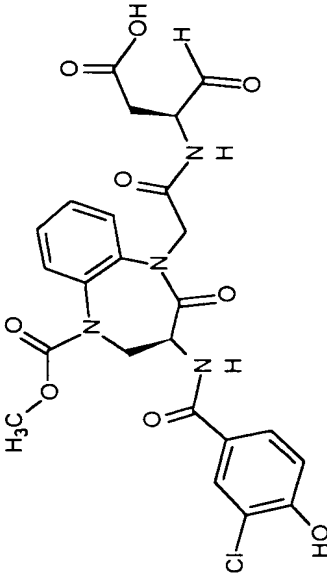
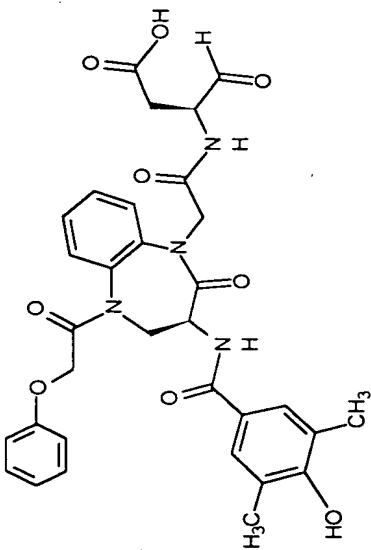
(3S)-3-[(3S)-2-Oxo-3-(2,4-dimethylthiazo-1-oyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid(801) was synthesized via methods used to prepare 2002 from 2001 to afford 801.

- 740 -

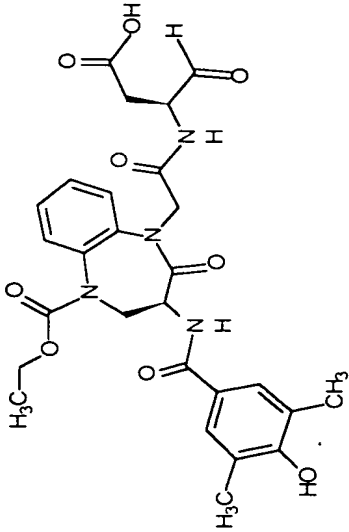
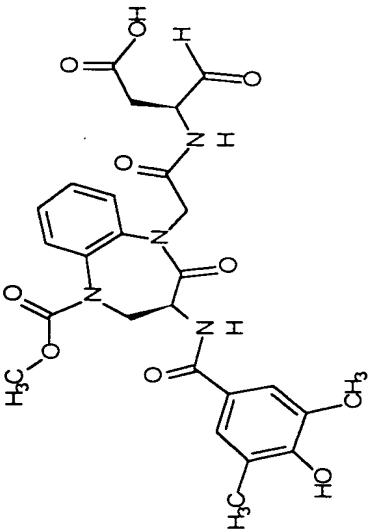
Example 34

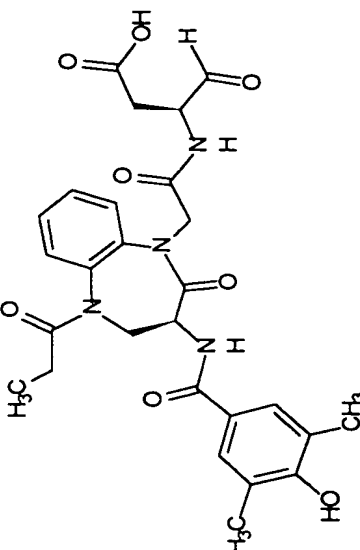
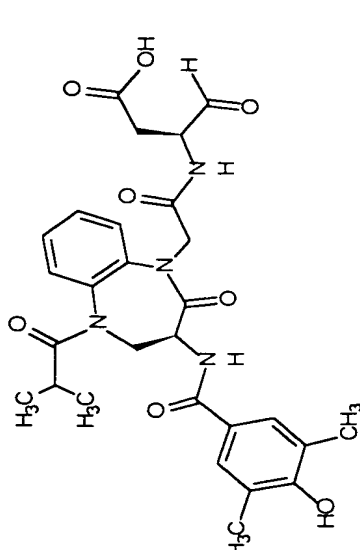
Compounds 720-73 were prepared by methods similar to the methods used to prepare compounds 619-635 (see, Example 13). Physical data for compounds
5 720-73 is listed in Table 29.

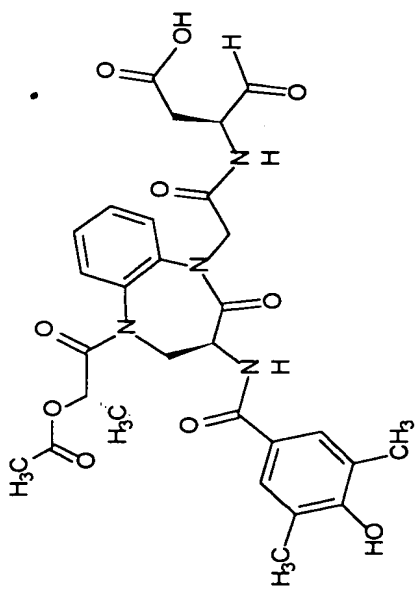
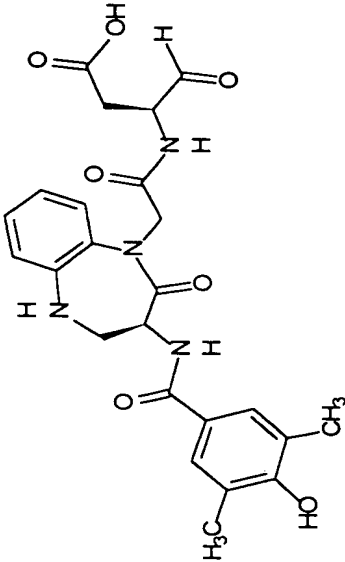
Table 29

Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na) +
720		C24H23ClN4O9	546.93	10.729 99%	568.8
721		C32H32N4O9	616.63	13.241 99%	640.4

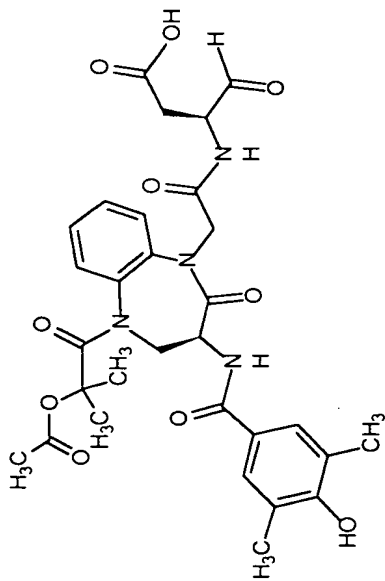
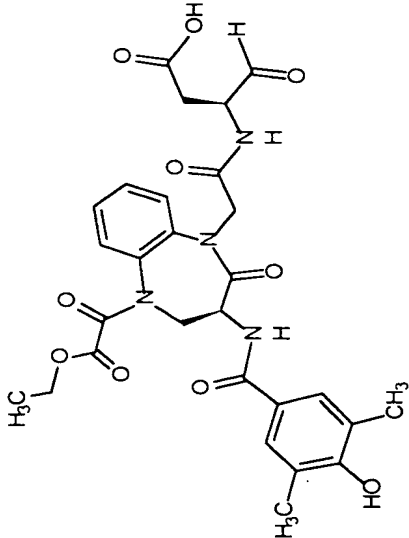
- 742 -

Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na)+
722		C27H30N4O9	554.56	11.761 99%	578.2
723		C26H28N4O9	540.53	10.655 79%	564.5

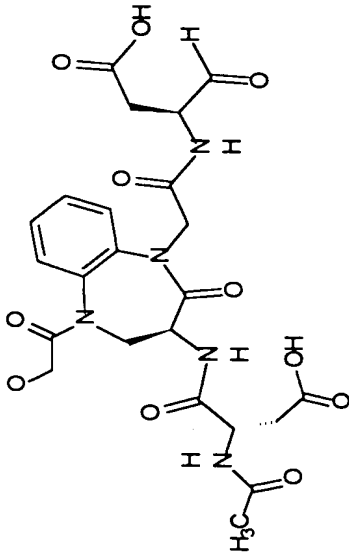
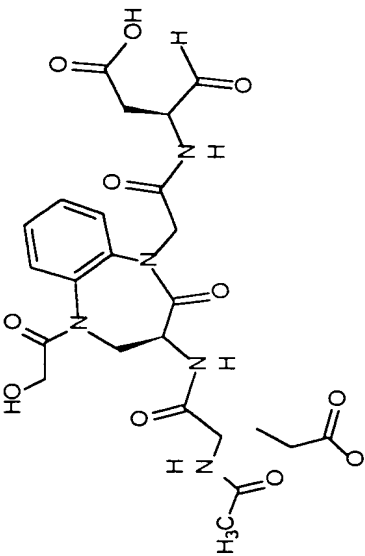
Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na) ⁺
724		C27H30N4O8	538.56	10.584 99%	563.1
725		C28H32N4O8	552.59	11.329 99%	577.2

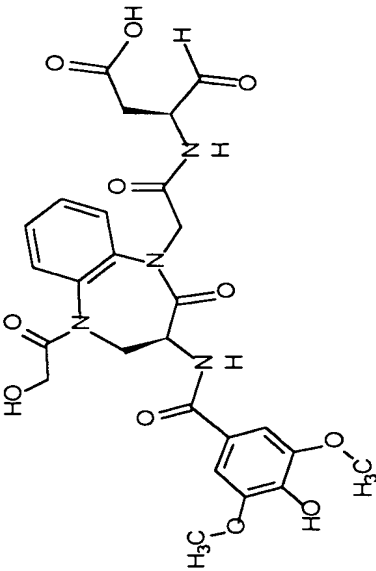
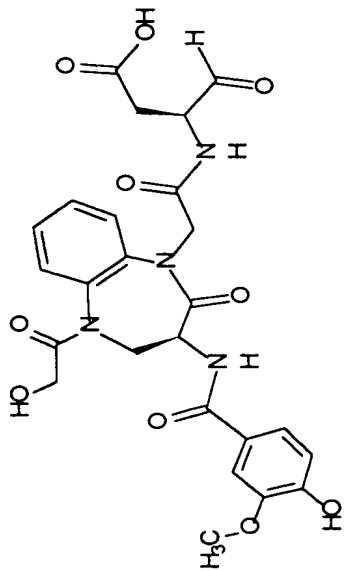
Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na) +
726		C29H32N4O10	596.60	10.667 99%	620.8
727		C24H26N4O7	482.50	9.085 92%	506.6

- 745 -

Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na)+
728		C30H34N4O10	610.63	11.556	634.9
729		C28H30N4O10	582.57	11.611 99%	607.3

- 746 -

Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na) +
730		C23H27N5O11	549.50	3.939 96%	572.2
731		C24H29N5O11	563.53	4.298 92%	587

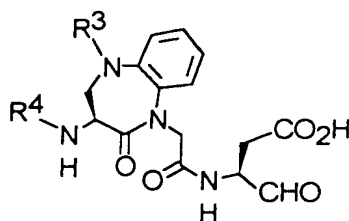
Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na) +
732		C26H28N4O11	572.53	7.640 98%	595.9
733		C25H26N4O10	542.51	7.375 98%	565.9

Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na)+
734		C32H28N6O7	608.62	9.656 99%	630.6
735		C28H27N5O9S	609.62	10.887 92%	632.1

- 749 -

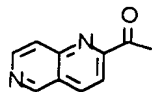
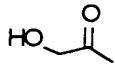
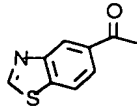
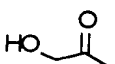
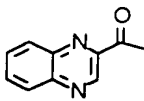
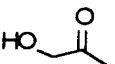
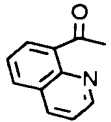
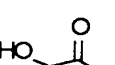
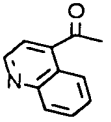
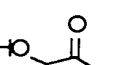
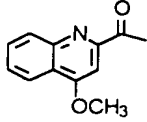
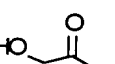
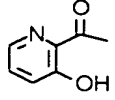
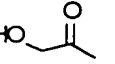
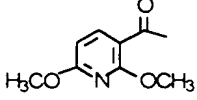
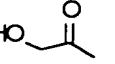
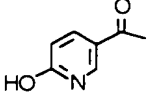
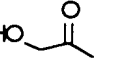
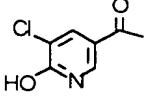
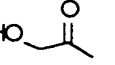
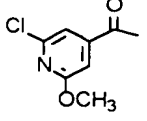
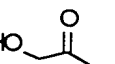
Example 35

Compounds **736-767** were prepared by methods similar to the methods used to prepare compounds **619-635** (see, Example 13). Physical data for compounds **736-767** is listed in Table 30.

Table 30

Compound	R ⁴	R ³
736		
737		
738		
739		
740		
741		

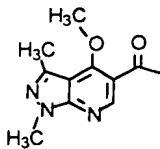
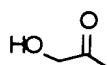
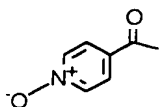
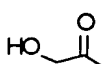
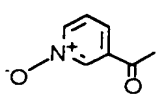
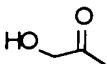
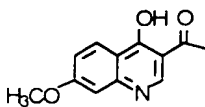
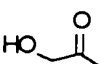
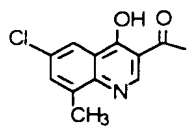
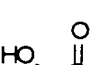
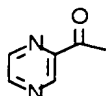
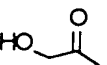
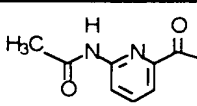
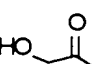
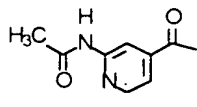
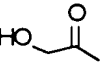
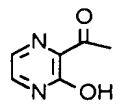
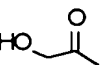
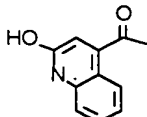
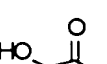
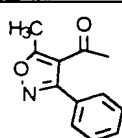
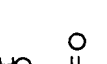
- 750 -

Compound	R ⁴	R ³
742		
743		
744		
745		
746		
747		
748		
749		
750		
751		
752		

5

10

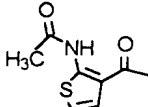
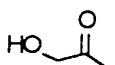
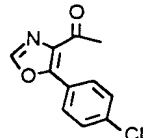
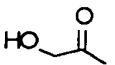
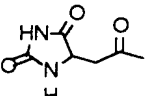
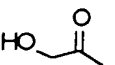
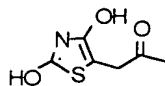
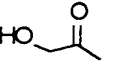
- 751 -

Compound	R ⁴	R ³
753		
754		
755		
756		
757		
758		
759		
760		
761		
762		
763		

5

10

- 752 -

Compound	R ⁴	R ³
764		
765		
766		
767		

5 The data of the examples above demonstrate that compounds according to this invention display inhibitory activity towards IL-1 β Converting Enzyme.

Insofar as the compounds of this invention are able to inhibit ICE in vitro and furthermore, may be delivered orally to mammals, they are of evident
10 clinical utility for the treatment of IL-1-, apoptosis-, IGIF-, and IFN- γ mediated diseases. These tests are predictive of the compounds ability to inhibit ICE in vivo.

15 While we have described a number of embodiments of this invention, it is apparent that our basic constructions may be altered to provide other embodiments which utilize the products and processes of this invention. Therefore, it will be appreciated that the scope
20 of this invention is to be defined by the appended claims, rather than by the specific embodiments which have been presented by way of example.